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International application number: PCT/US05/009294

International filing date: 17 March 2005 (17.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/621,162
Filing date: 22 October 2004 (22.10.2004)

Date of receipt at the International Bureau: 09 May 2005 (09.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
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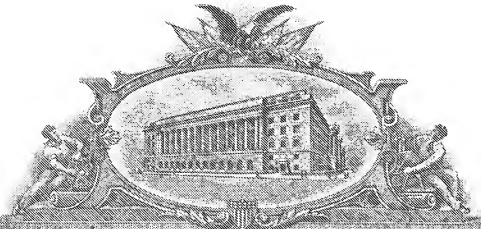

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APPLICATION NUMBER: ***60/621,162***
FILING DATE: ***October 22, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US05/09294***

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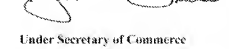

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Modified PTO/SB/16 (6-95)
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Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-16723A	Type a plus sign (+) inside this box -->	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE NAME	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Mantlo	Nathan	Bryan	Brownsburg, Indiana
Wang	Xiaodong		Carmel, Indiana

TITLE OF THE INVENTION (280 characters max)

COMPOUNDS AND METHODS FOR TREATING DYSLIPIDEMIA

CORRESPONDENCE ADDRESS

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

25885
PATENT TRADEMARK OFFICE

STATE	IN	ZIP CODE	46206-6288	COUNTRY	USA

ENCLOSED APPLICATION PARTS (*check all that apply*)

X	Specification	Number of pages	81		Small Entity Statement
	Drawing(s)	Number of Sheets			Other (Specify)

METHOD OF PAYMENT (*check one*)

	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT ($)	$160.00
X	The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

X No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,
SIGNATURE Francis O. Ginah Date 10/22/04

TYPED or PRINTED NAME FRANCIS O. GINAH

REGISTRATION NO. (*if appropriate*) 44,712

☐ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

"Express Mail" mailing label number EV 392094530 US Date of Deposit October 22, 2004
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450.

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COMPOUNDS AND METHODS FOR TREATING DYSLIPIDEMIA

FIELD OF THE INVENTION

The current invention relates to the fields of medicinal organic chemistry, pharmacology, and medicine. Further, the current invention relates to a group of compounds that demonstrate utility for treating pathological states due to dyslipidemia

BACKGROUND OF THE INVENTION

Coronary heart disease (CHD) is one of the major causes of morbidity and mortality worldwide. Despite attempts to modify risk factors such as obesity, smoking, lack of exercise, and treatment of dyslipidemia with dietary modification or drug therapy, CHD remains the most common cause of death in the U.S. Over 50% of all CHD deaths are due to underlying atherosclerotic coronary heart disease.

Dyslipidemia is a major risk factor for CHD. Low plasma levels of high density lipoprotein (HDL) cholesterol with either normal or elevated levels of low density (LDL) cholesterol is a significant risk factor for developing atherosclerosis and associated coronary artery disease in humans. Indeed, several studies on lipoprotein profiles of CHD patients have shown that about 50% of the CHD patients have cholesterol levels that are considered to be in the normal range (<200 mg/dl). Furthermore, these studies found low HDL cholesterol in about 40% of the normo-cholesterolemic CHD patients as compared to the general population reported in the National Health and Nutrition Examination Survey. Since low levels of HDL cholesterol increase the risk of

atherosclerosis, methods for elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of cardiovascular disease including, but not limited to, atherosclerosis, CHD, stroke, and peripheral vascular disease.

Cholesterol ester transfer protein (CETP) is a 74 KD glycoprotein that facilitates the exchange of cholesterol esters in HDL for triglycerides in triglyceride-rich lipoproteins (A. R. Tall et. al., (1999) 1999 George Lyman Duss Memorial Lecture: Lipid transfer proteins, HDL metabolism and atherogenesis. *Arterio. Thromb. Vasc. Biol.* 20:1185-1188.). The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be proatherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD. Niacin can significantly increase HDL, but has serious toleration issues that reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL cholesterol only modestly (~10-12%). As a result, there is a significant unmet medical need for a well-tolerated agent that can significantly elevate plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis.

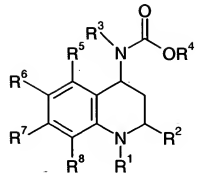
CETP is expressed in multiple tissues and secreted into plasma, where it associates with HDL (X.C. Jiang et. al., (1991) Mammalian adipose tissue and muscle are major sources of lipid transfer protein mRNA. *J. Biol. Chem.* 266:4631-4639). Humans and monkeys, which express CETP, have relatively low HDL cholesterol, whereas mice and rats do not express CETP and carry nearly all their cholesterol in HDL. Further more, transgenic expression of CETP in mice results in significantly reduced HDL cholesterol levels and developed severe atherosclerosis compared to control mice (K.R. Marotti et. al., (1993) Severe atherosclerosis in transgenic mice expressing simian cholesteryl ester transfer protein. *Nature*:364, 73-75). Expression of human CETP in Dahl salt-sensitive hypertensive rats led to spontaneous combined hyperlipidemia, coronary heart disease and decreased survival (V.L.M. Herrera et. al., (1999) Spontaneous combined hyperlipidemia, coronary heart disease and decreased survival in Dahl salt-sensitive hypertensive rats transgenic for human cholesteryl ester transfer protein. *Nature Medicine*: 5, 1383-1389).

Antibodies either directly injected into the plasma or generated through vaccine injection can effectively inhibit CETP activity in hamsters and rabbits resulting in

elevated HDL cholesterol (C. W. Rittershaus, (1999) Vaccine-induced antibodies inhibit CETP activity in vivo and reduce aortic lesions in a rabbit model of atherosclerosis. Furthermore, antibody neutralization of CETP in rabbits has been shown to be anti-atherogenic (*Arterio. Thromb. Vasc. Biol.* 20, 2106-2112;G.F.Evans et. al., (1994) Inhibition of cholesteryl ester transfer protein in normocholesterolemic and hypercholesterolemic hamsters: effects on HDL subspecies, quantity, and apolipoprotein distribution. *J. Lipid Research.* 35, 1634-1645). However, antibody and/or vaccine therapy is not currently a viable option for the treatment of large populations of patients in need of treatment for dyslipidemia and resultant or associated disease state manifestations.

There have been several reports of small molecule CETP inhibitors. Barrret et. al. (J.Am Chem. Soc., 188, 7863, (1996)) and Kuo et al. (J. Am. Chem. Soc.,117, 10629, (1995)) describe cyclopropan-containing CETP inhibitors. Pietzonka et al. (Biorg. Med. Chem. Lett. 6, 1951 (1996)) describe phosphanate-containing analogs as CETP inhibitors. Coval et al. (Bioorg. Med. Chem. Lett. 5, 605, (1995)) describe Wiedendiol-A and –B related sesquiterpines as CETP inhibitors. Japanese Patent Application No. 10287662-A describes polycyclic, non-amine containing, polyhydroxylic natural compounds possessing CETP inhibition properties. Lee et al. (*J. Antibiotics,* 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (*Lipids,* 25, 216-220 (1990)) describe cholesteryl acetyl bromide as a CETP inhibitor. Morton and Zillversmit (*J. Lipid Res.,* 35, 836-47 (1982)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP. Connolly et al. (*Biochem. Biophys. Res. Comm.* 223, 42-47 (1996)) describe other cysteine modification reagents as CETP inhibitors. Xia et al. Describe 1,3,5-triazines as CETP inhibitors (*Bioorg. Med. Chem. Lett.,* 6, 919-22 (1996)). Bisgaier et al. (*Lipids,* 29, 811-8 (1994) describe 4-phenyl-5-tridecyl-4H-1,2,4-triazole-thiol as a CETP inhibitor. Oomura et al. Disclose non-peptidic tetracyclic and hexacyclic phenols as CETP inhibitors in Japanese Patent Application No. 10287662.

United States patent No.6,586,448 B1 describes 4-caboxamino-2-substituted-1,2,3,4-tetrahydroquinolines of formula I



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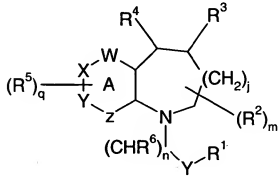
and prodrugs thereof, and pharmaceutically acceptable salts of said compounds and said prodrugs; wherein R^1,R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined therein. Similarly, PCT patent applications WO 03/063868A1, WO 0017164, No.0017165, and WO 0017166, discloses variously, formulations, methods of preparation and methods of use of tetrahydroquinoline compounds generally related to that of U.S patent 6,586,448 B1 from which it derives or is a divisional application thereof.

European Patent Application No. 818448 by Schmidt et al. describes tetrahydroquinoline derivatives as cholesteryl ester transfer protein inhibitors. European Patent Application No. 818197, Schmek et al. describe pyridines with fused heterocycles as cholesteryl ester transfer protein inhibitors. Brandes et al. in German Patent Application No. 19627430 describe bicyclic condensed pyridine derivatives as cholesteryl ester transfer protein inhibitors. In US Patent 6,207,671 Schmidt et al., describe substituted pyridine compounds as CETP inhibitors. In WO Patent Application No. 09839299, and WO Patent application No.03028727 by Muller-gliemann et al. and Erfinder/Anmelder respectively, describe quinoline derivatives as cholesteryl ester transfer protein inhibitors.

The above disclosures notwithstanding, a great need remains for effective compounds useful to treat conditions caused by, associated with or exacerbated by dyslipidemia.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



wherein

n is 0, 1, 2, or 3;

m is 0, 1, 2, 3, 4, 5 or 6;

j is 0, 1, or 2;

q is 0, 1, or 2;

W, X, Y and Z are each independently CH, C, N, S, or O with appropriate single or double bonds and/or hydrogen atoms to complete valency requirements;

Ring A is a five or six member ring wherein one of W, X, Y or Z may be absent; provided that ring A is not phenyl;

Y is a bond, C=O, or $S(O)_p$;

p is 0, 1 or 2;

R^1 is selected from a group consisting of hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, C_1-C_6 alkylheterocyclic, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl; C_1-C_6 alkylaryl, aryl, heterocyclyl, C_2-C_6 alkylalcohol, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -OC_1-C_6 alkylheterocyclic, -OC_3-C_8 cycloalkyl, -OC_1-C_6 alkylcycloalkyl, -NR^7R^8, -OC_1-C_6 alkylaryl, -O-heterocyclic, $CONR^{11}R^{12}$, $NR^{11}SO_2R^{12}$, $NR^{11}COR^{12}$, C_0-C_3 alkyl$NR^{11}R^{12}$, C_1-C_3 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$and -OC_1-C_6 alkylheterocyclic; provided that R^1 is not hydroxy when Y is $S(O)_p$, CO, or when n and y are both zero; and wherein each cycloalkyl, aryl or heterocyclic group is optionally substituted with 1 to 3 groups independently selected from oxo, hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy,

$CONR^{11}R^{12}$, $NR^{11}SO_2R^{12}$, $NR^{11}COR^{12}$, C_0-C_3 alkyl$NR^{11}R^{12}$, C_1-C_3 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, cyano, C_1-C_6 alkylcycloalkyl, phenyl, -OC_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylaryl, -OC_1-C_6 alkylheterocyclic, and C_1-C_6 alkylaryl;

R^2 is independently selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OC_1-C_6 alkyl, C_1-C_6 alkylaryl, aryl, C_0-C_6 alkylNR^7R^8, heteroaryl, heterocyclyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl and C_1-C_6 alkylheterocyclyl; wherein each cycloalkyl, aryl, or heterocyclic is optionally substituted with 1 to 3 groups independently selected from oxo, hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alcohol, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $CONR^{11}R^{12}$, $NR^{11}SO_2R^{12}$, $NR^{11}COR^{12}$, C_0-C_3 alkyl$NR^{11}R^{12}$, C_1-C_3 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, cyano, and phenyl, and wherein two R^2 groups may combine to form a 3,4 or 5 member spirocycle, or a five or six member fused carbocyclic or heterocyclic ring;

R^3 is hydrogen, C_1-C_6 alkyl, aryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, C_3-C_8 cycloalkyl, or C_1-C_6 alkylcycloalkyl;

R^4 is hydrogen, C_1-C_6 alkyl, aryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl or a group represented by the formula -NR^9R^{10};

R^5 is selected from the group consisting of hydrogen, hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, aryl, C_1-C_6 alkylaryl, heteroaryl, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -NR^7R^8, and -OC_1-C_6 alkylaryl; and wherein when q is 1, 2 or 3, two adjacent R5 groups may combine to form a fused 5 or 6 member optionally substituted carbocyclic or heterocyclic ring;

R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, C_1-C_6 alkylNR^7R^8, C_3-C_8 cycloalkyl, and C_1-C_6 alkylcycloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, C_1-C_6 alkyheterocyclic, heterocyclic, aryl, C_1-C_6 alkylaryl, wherein each alkyl, heterocyclic, or aryl group is optionally substituted with 1-3 groups independently selected from halogen, C_1-C_6 alkycylcloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylheterocyclic, C_1-C_6 haloalkyl, and $NR^{11}R^{12}$; or R^7 and R^8 combine to form a nitrogen containing heterocyclic ring which may have 0,

1, or 2 additional hetero-atoms selected from oxygen, nitrogen or sulfur and may be optionally substituted with oxo, or C_1-C_6 alkyl;

R^9 is the group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, aryl, heterocyclic, C_1-C_6 alkylheterocyclic, COR^7, CO_2R^7, $CONR^7R^8$, $S(O)_pNR^7R^8$, or $S(O)_pR^7$ wherein R^7 is as defined above, and wherein each alkyl, cycloalkyl, aryl, and heterocyclic is optionally substituted with one to two groups independently selected from halo, hydroxy, oxo, COOH, $C(O)OC_1$-C_4 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylalcohol, C_1-C_6 alkylamine, C_1-C_6 alkylaryl, C_2-C_6 alkenylaryl, C_2-C_6 alkynylaryl, C_1-C_6 alkylheterocyclic, $-NR^7R^8$, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, C_1-C_6 alkyl-O-C_1-C_6 alkylaryl, C_1-C_6 alkyl-NR^2-C_1-C_6 alkylaryl, and aryl, wherein each cycloalkyl or aryl group is optionally substituted with halo, hydroxy, oxo, amino, COOH, $C(O)OC_1$-C_4 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylalcohol, and C_1-C_6 alkylamine;

R^{10} is selected from the group consisting of aryl, C_1-C_6 alkylaryl, C_2-C_6 alkenylaryl, C_2-C_6 alkynylaryl, C_1-C_6 haloalkylaryl, C_1-C_6 alkylheterocyclic, C_2-C_6 alkenylheterocyclic, C_1-C_6 alkylcycloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkyl-O-C_1-C_6 alkylaryl, and wherein each cycloalkyl, aryl, or heterocyclic group is optionally substituted with 1-3 groups independently selected from the group consisting of hydroxy, oxo, $-SC_1$-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 haloalkyl, halogen, C_1-C_6 alkoxy, aryloxy, C_1-C_6 alkenyloxy, C_1-C_6 haloalkoxyalkyl, C_0-C_6 alkyl$NR^{11}R^{12}$, $-OC_1$-C_6 alkylaryl, nitro, cyano, C_1-C_6 haloalkylalcohol, and C_1-C_6 alkylalcohol;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl, heterocyclic, aryl, and C_1-C_6 alkylaryl, wherein each aryl group is optionally substituted with 1-3 groups independently selected from halogen, C_1-C_6 alkylheterocyclic, and C_1-C_6 haloalkyl, or R^{11} and R^{12} combine to form a nitrogen containing heterocyclic ring which may have 0, 1, or 2 additional heteroatoms selected from oxygen, nitrogen or sulfur and is optionally substituted with oxo, or C_1-C_6 alkyl; or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

The present invention also provides a method for modulating or regulating CETP activity comprising the use of a compound of formula I or a pharmaceutically acceptable

salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof, for the treatment, prevention or amelioration of CETP mediated diseases.

The present invention provides a method for treating or preventing dyslipidemia comprising administering a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating or preventing CHD comprising administering a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating and/or preventing artherosclerosis comprising administering a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating and/or preventing diseases related to abnormal CETP activity comprising administering a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of raising the ratio of plasma HDL-cholesterol to plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of raising the level of plasma HDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of lowering the level of plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof, and a carrier.

The present invention also provides a method of treating and/or preventing the pathological sequelae due to low levels of plasma HDL and/or high levels of LDL-cholesterol in a mammal comprising administering an effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers, thereof, to a patient in need thereof.

The present invention also relates to the use of a compound of formula I for the manufacture of a medicament for treating and/or preventing atherosclerosis in a mammal comprising administering an effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention also provides a combination therapy involving a compound of formula I and one or more other effective cardio protective agents such as, for example, statins, leptin, and/or other LXR, CETP, ABC A1 or lipid regulating agents useful for the treatment and/or prevention of atherosclerosis.

DETAILED DESCRIPTION OF THE INVENTION

The current invention provides novel compounds of formula I useful in modulating CETP activity.

The terms "modulation" or "regulating" would include, but not be limited to, up-regulation, down-regulation, inhibition, agonism, antagonism of the CETP receptor as appropriate to achieve HDL raising, or LDL lowering and the resulting biological sequelae from such intervention.

The phrase "diseases" or "diseases related to abnormal activity CETP" or "diseases mediated by CETP activity" refers to pathological states where atherosclerosis and/or other cardiovascular diseases are prone because of dyslipidemia and/or other risk factors and are therefore beneficially affected by modulation, particularly down-regulation, of CETP activity. These diseases include but are not limited to hyperlipidemia and its sequelae such as atherosclerosis, CHD, elevated blood pressure, CHF, stroke, hypertension, hypertriglyceremia, diabetes, obesity, inflammatory diseases

including but not limited to dermatitis, arthritis, and pain, and diseases of the central nervous system including but not limited to dementia, cognitive disorders such as, for example, Alzheimer's disease.

The term "treatment" bears its usual meaning which includes prohibiting, inhibiting, ameliorating, halting, restraining, slowing or reversing the progression, or reducing the severity of a pathological symptom related to or resultant from the modulation of CETP activity, especially as related to raising plasma levels of HDL, or lowering LDL-cholesterol levels or raising the HDL/LDL ratio or controlling atherosclerosis, hyperlipidemia and/or hypercholesterolemia.

Generally, one of skill in the art is aware that valency must be conserved (complete) for all stable molecules. Therefore, the necessary implication that hydrogen atoms are necessary and available to complete valency in all structures including formula I unless expressly indicated otherwise, is imputed to the general knowledge of one of skill in the art.

General chemical terms used in the description of compounds herein described bear their usual meanings. For example, the term "C_{1-6} alkyl," or "(C_1-C_6)alkyl" or "C_1-C_6 alkyl" refers to a straight or branched aliphatic chain of 1 to 6 carbon atoms including but not limited to methyl, ethyl, propyl, iso-propyl, n-butyl, pentyl, and hexyl. Unless otherwise stated, the term "alkyl" means C_1-C_6 alkyl. Similarly, the term "C_0-C_6 alkyl" implies an alkyl group as indicated wherein when the term C_0 applies, the alkyl group is not present, and the remaining groups attach directly to the substrate. The invention also contemplates that the term C_1-C_6 alkyl or C_2-C_6 alkenyl or similar terms also encompass the specified alkyl or alkenyl or similar group, which may be chiral, regio or steroisomeric. Such chiral or regio or stereoisomeric groups are also objects of the present invention.

The term "alkylaryl" refers to an alkyl group substituted by an aryl group. For example, C_1-C_6 alkylaryl indicates that a C_1-C_6 alkyl group is attached to the aryl group, and that the resulting C_1-C_6 alkylaryl is attached to the nucleus via the alkyl group. Preferred alkylaryl group include phenyl ethyl (phenethyl)benzyl.

The term "substituted phenyl" or "optionally substituted phenyl" refers to a phenyl group having one or more substituents selected from the group consisting of C_1-C_6 alkyl,

C_1-C_6 alkoxy, hydroxy, COR^7, -$COOR^7$, C_0-C_6 alkylNR^7R^8, nitro, chloro, fluoro, bromo, iodo, C_1-C_6haloalkyl, C_1-C_6 haloalkoxyalkyl, and C_0-C_6 alkylheterocyclic.

The term "optionally substituted carbocyclic or heterocyclic ring" refers to a saturated or unsaturated, aromatic or non-aromatic five or six member ring having optional substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, COR^7, -$COOR^7$, C_0-C_6 alkylNR^7R^8, nitro, chloro, fluoro, bromo, iodo, C_1-C_6haloalkyl, C_1-C_6 haloalkoxyalkyl, and C_0-C_6 alkylheterocyclic.

The term "aryl" refers to a substituted or unsubstituted aromatic or heteroaromatic carbocyclic or heterocyclic radical. Illustrative aryl groups include but is not limited to napthyl, quinolyl, tetrahydroquinolyl, indazolyl, pyrimidinyl, triazinyl, pyrazine, pyridazinyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, pyranyl, tetrazolyl, imidazolyl, 1,2,3-trazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazopyridine, benzimidazolyl, triazolone-yl, imidazolone-yl, imidazolidinone-yl, 2-furyl, 3-furyl, 2-thienyl 3- thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 2-benzofuryl, 3-benzofuryl, 4-benzofuryl, 5-benzofuryl, 6-benzofuryl, 7-benzofuryl, 2-benzothieny, 3-benzothienyl, 4-benzothienyl, 5-benzothienyl, 6-benzothienyl, 7-benzothienyl, 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, tetrazole , imidazole, isoxazole, pyrazole, 7-indolyl, and isomers thereof. As used herein the term aryl also encompasses the benzyl group.

The term "C_3-C_8 cycloalkyl" or similar terms refer to a saturated carbocyclic ring having from 3 to 8 carbon atoms where the term "cycloalkyl" is used a carbocyclic ring having 3 to 8 carbon atoms is implied.

The term "carbocycle" as used herein refers to a cyclic group having only carbon and appropriate number of hydrogen atoms. The term encompasses groups such as cycloalkyl, cycloalkene, cycloalkylene, naphthyl, phenyl and the like.

The term "heterocycle", "heterocyclyl", or "heterocyclic" refers to a 5, 6, 7, 8, 9 or 10 member saturated, partially unsaturated, or aromatic, mono-cyclic or a bicyclic ring containing 1-5 heteroatoms selected from N, S or O, wherein said heterocycle is optionally substituted at carbon or nitrogen atom(s) unless otherwise specified. Most preferred heterocyclic groups include pyridinyl, pyrolidinyl, piperidinyl,

hexamethyleneimmino, morpholino, thiophene, indolyl, quinolyl, isoquinolyl, tetrazolyl, and pyridinyl.

As a corollary, the term "alkylheterocyclic" or "alkylheterocycle" is understood to mean that the alkyl group is attached to the heterocycle and the point of attachment to the molecular backbone or nucleus is the alkyl group. The term "alkyl" without a qualifier implies a C_1-C_6 alkyl group.

The term "haloalkoxyalkyl" as used herein include for example trifluoromethoxy, pentafluoroethoxy, trifluoroethoxy (OCH_2CF_3) and the like.

The term "Prodrugs" describes derivatives of the compounds of the invention that have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives, such as, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic esters (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl) or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. Other preferred esters include morpholinoethyloxy, diethylglycolamide and diethylaminocarbonylmethoxy. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters.

As used herein, the term "protecting group" refers to a group useful for masking reactive sites in a molecule to enhance the reactivity of another group or allow reaction at another desired site or sites following which the protecting group may be removed. Protecting groups are usually used to protect or mask groups including but not limited to -OH, -NH, and –COOH. Suitable protecting groups are known to one of skill in the art and are described in Protecting groups in Organic Synthesis, 3rd edition, Greene, T. W.; Wuts, P.G.M. Eds., John Wiley and Sons, New York, 1999.

As used herein, the term "solvate" is a form of the compound of the invention wherein a crystal or crystals of a compound of the invention have been formed from a

stoichiometric or non-stoichiometric amount of the compound of formula I and a solvent. Typical solvating solvents include for example, water, methanol, ethanol, acetone and dimethylformamide.

In those instances where a compound of the invention possesses acidic or basic functional groups, various salts may be formed which are more water soluble and/or more physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion-exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base or acid addition salts of compounds of the present invention. Base addition salts include for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, hydrobromide, camsylate, carbonate, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrochloride, hydroxynaphthoate, hydroiodide, isothionate, lactate, lactobionate, laureate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate. Preferred salts for the purpose of the invention include the hydrochloride salt, the hydrobromide salt, the bisulfate salt, the methane sulfonic acid salt, the *p*-toluenesulfonic acid salt, bitartrate, the acetate and the citrate salt.

A compound of the invention as illustrated by formula I may occur as any one of its positional isomers, stereochemical isomers or regio-isomers, all of which are objects of the invention. Certain compounds of the invention may possess one or more chiral centers, and thus, may exist in optically active forms. Likewise, when the compounds

contain an alkenyl or alkenylene group, there exist the possibility of cis- and trans-isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of enantiomers or cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereo-specific reactions with starting materials that contain the asymmetric centers and are already resolved. Alternatively desired stereoisomers may be prepared by methods that lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound i.e. a chiral resolving agent. This changes the racemic form into a mixture of stereoisomers and diastereomers, because they have different melting points, different boiling points, and different solubilities and can be separated by conventional means, such as crystallization.

Preferred Embodiments of The Invention

Preferred n, m, p, j and q

Preferably n is 0, or 1. More preferably, n is 0.

Preferably m is 0, 1, 2 or 3. More preferably m is 0, 1 or 2.

Preferably p is 1, or 2.

Preferably j is 0, 1 or 2;

Preferably, q is 0, 1 or 2. More preferably q is 0 or 1. Most preferably, q is 0.

Preferred A ring

A preferred a ring is selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, 1,2,5-triazine, thiophene, furan, pyrrole, pyrazole, isoxazole, isothiazole, imidazole, oxazole, thiazole, and 1,2,3-triazole. More preferred is an A ring selected from the group consisting of pyridine, pyrazine, thiophene, pyrazole, isoxazole, oxazole, and thiazole.

Preferred R^1

A preferred R^1 groups is selected from the group consisting of hydrogen, -C_1-C_6 alkyl, -OC_1-C_6 alkoxy, C_1-C_6 alkylaryl, -OC_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylcycloalkylNR^7R^8, C_1-C_6 alkoxy, -OC_1-C_6 alkylaryl, and -OC_1-C_6 alkylheterocyclic provided that when y is $S(O)_pR^7$, R^1 is not hydrogen. More preferred is an R^1 group selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, -OC_1-C_6 alkylaryl, and -OC_0-C_6 alkylcycloalkylNR^7R^8. Most preferred is an R^1 group represented by C_1-C_6 alkoxy.

Preferred R^2

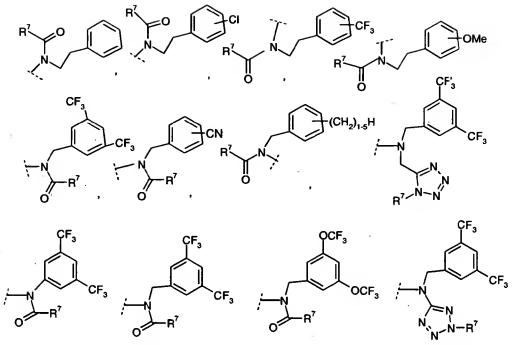
A preferred R^2 groups is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 haloalkyl, halo, C_1-C_6 alkylhalide, -C_1-C_6 alkylcycloaryl, C_1-C_6 alkylaryl, -OC_1-C_6 alkyl, -OC_1-C_6 haloalkyl, -OC_1-C_5 alkylcycloalkyl, C_0-C_6 alkylNR^7R^8, -OC_1-C_6 alkylaryl, -C_1-C_6 alkylheterocyclic, and -OC_1-C_6 alkylheterocyclic. More preferred is an R^2 group selected from hydroxy, C_1-C_6 alkyl, halo, C_1-C_6 alkylaryl and C_1-C_6 alkoxyalkyl. Most preferred is an R^2 group represented by hydrogen or C_1-C_6 alkyl.

Preferred R^3 Groups

Preferably R3 is hydrogen.

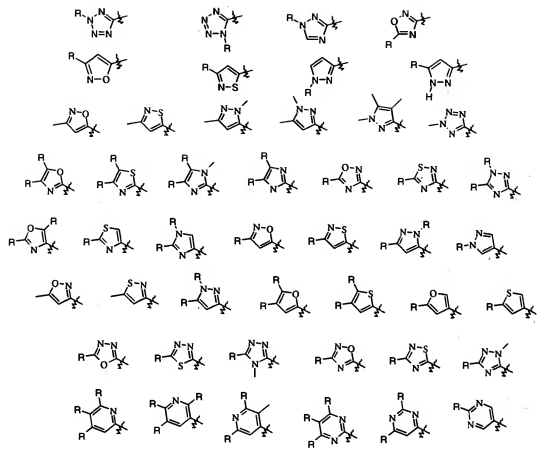
Preferred R^4 Groups

A preferred R^4 group is NR^9R^{10}. Preferably, the group $-NR^9R^{10}$ is represented by a group selected from the group consisting of:



Also preferred are R^9 groups selected from the group consisting of COR^7, CO_2R^7, $CONR^7R^8$, $S(O)_2NR^7R^8$, or $S(O)R^7$ wherein R^7 is as defined above.

More preferably, R^4 is NR^9R^{10}, wherein R^{10} is a mono or di-substituted haloalkylbenzyl, and R^9 is heterocyclic selected from the group consisting of:



wherein R is H, OH, NR^7R^8 or C_1-C_3 alkyl wherein C_1-C_3 alkyl group is optionally substituted with OH, halo, or NR^7R^8.

Preferred R^5 groups

R^5 is preferably selected from a group consisting of hydrogen, hydroxy, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkylheterocyclcic, C_1-C_6 alkylaryl, aryl, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -$CH_2NR^7R^8$, -NH_2, -CN, -COOH, and NO_2; More preferably, R^5 is at each occurrence independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy.

Preferred R^6

R^6 is preferably selected from a group consisting of hydrogen, hydroxy, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkylheterocyclcic, C_1-C_6 alkylaryl, aryl, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -$CH_2NR^7R^8$, -NH_2, -CN, -COOH, and NO_2;

More preferably, R^6 is at each occurrence independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy.

Preferred R^7 and R^8

Preferred R^7 and R^8 are independently selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkylaryl, and C_1-C_6alkylheterocyclic, wherein each aryl group is optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl, halo, and C_1-C_6 haloalkyl.

Preferred R^{11} and R^{12}

Preferred R^{11} and R^{12} are independently selected from a group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkylaryl, and C_1-C_6alkylheterocyclic, wherein each aryl group is optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl, halo, and C_1-C_6 haloalkyl.

A most preferred compound of the invention is a compound selected from the group consisting of:

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-3,4-dihydro-2H-[1,7]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-3,4-dihydro-2H-[1,6]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-methyl-2-ethyl-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5-ethyl-3,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-4-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5-ethyl-2,5,6,7-tetrahydro-pyrazolo[4,3-b]pyridine-4-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5-ethyl-6,7-dihydro-5H-2-thia-4-aza-indene-4-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-5,6-dihydro-4H-thieno[2,3-b]pyridine-7-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-5,6-dihydro-4H-isoxazolo[5,4-b]pyridine-7-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-3-trifluoromethyl-5,6-dihydro-4H-isoxazolo[5,4-b]pyridine-7-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-3-methyl-5,6-dihydro-4H-isoxazolo[5,4-b]pyridine-7-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-3-isopropyl-5,6-dihydro-4H-isoxazolo[5,4-b]pyridine-7-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-ethyl-6,7-dihydro-5H-pyrido[2,3-d]pyrimidine-8-carboxylic acid isopropyl ester,

8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-7,8-dihydro-6H-pyrido[2,3-b]pyrazine-5-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-bromo-5-ethyl-6,7-dihydro-5H-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-trifluormethyl-5-ethyl-6,7-dihydro-5H-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-chloro-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-methyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-trifluoromethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-methoxy-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-methyl-3,4-dihydro-2*H*-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-chloro-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-4,5,6,7-tetrahydro-thieno[2,3-b]azepine-8-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-bromo-4,5,6,7-tetrahydro-thieno[2,3-b]azepine-8-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3-trifluoromethyl-4,5,6,7-tetrahydro-thieno[2,3-b]azepine-8-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester,

8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3-methyl-5,6,7,8-tetrahydro-thieno[3,2-b]azepine-4-carboxylic acid isopropyl ester,

8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-bromo-5,6,7,8-tetrahydro-thieno[3,2-b]azepine-4-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-4,5,6,7-tetrahydro-pyrazolo[2,3-b]azepine-8-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-4,5,6,7-tetrahydro-isoxazolo[5,4-b]azepine-8-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-pyrido[2,3-b]azepine-9-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-pyrido[3,4-b]azepine-1-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-pyrido[4,3-b]azepine-1-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-pyrido[3,2-b]azepine-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-trifluoromethyl-6,7,8,9-tetrahydro-pyrido[3,2-b]azepine-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3-trifluoromethyl-6,7,8,9-tetrahydro-pyrido[3,2-b]azepine-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-1,4,5-triaza-benzocycloheptene-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-trifluoromethyl-6,7,8,9-tetrahydro-1,4,5-triaza-benzocycloheptene-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-chloro-6,7,8,9-tetrahydro-1,4,5-triaza-benzocycloheptene-5-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-pyrimido[4,5-b]azepine-9-carboxylic acid isopropyl ester,

8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-3H-1,3,4-triaza-azulene-4-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3,5,6,7,8,9-hexahydro-1,3,4-triaza-cyclopentacyclooctene-4-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-1,4,5,6,7,8-hexahydro-1,2,9-triaza-cyclopentacyclooctene-9-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-4H-1-oxa-2,9-diaza-cyclopentacyclooctene-9-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-4H-thieno[2,3-b]azocine-9-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-5H-2-thia-4-aza-cyclopentacyclooctene-4-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-5H-1,10-diaza-benzocyclooctene-10-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-5H-2,10-diaza-benzocyclooctene-10-carboxylic acid isopropyl ester,

10-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7,8,9,10-tetrahydro-6H-2,5-diaza-benzocyclooctene-5-carboxylic acid isopropyl ester,

10-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7,8,9,10-tetrahydro-6H-1,5-diaza-benzocyclooctene-5-carboxylic acid isopropyl ester,

10-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7,8,9,10-tetrahydro-6H-1,4,5-triaza-benzocyclooctene-5-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-5H-1,3,10-triaza-benzocyclooctene-10-carboxylic acid isopropyl ester,

Cis-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester ,

Cis-4-[(3,5-bis-trifluoromethyl-benzyl)-(2*H*-tetrazol-5-yl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester,
Cis-4-[(3,5-bis-trifluoromethyl-benzyl)-(2-methyl-2*H*-tetrazol-5-yl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester,
or a pharmaceutically acceptable salt, solvate enantiomer or diastereomer or mixture thereof.

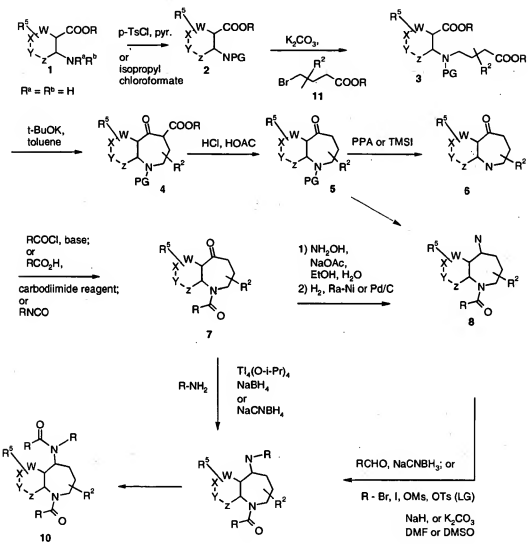
The positional isomers issues, and geometric isomers associated with the asymmetric carbon atoms of compounds of formula I are also contemplated to be within the scope of the current invention as useful for the treatment of diseases related to CETP modulation.

Synthesis of Compounds of the Invention

The compounds of the instant invention can be synthesized as exemplified in schemes 1–12. Aryl amino ester intermediates of Formula 1 can be chemically prepared, for example, by following the synthetic routes set forth in the Schemes below. However, the following discussion is not intended to be limiting to the scope of the present invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art. Other necessary reagents and starting materials may be made by procedures which are selected from standard techniques of organic and heterocyclic chemistry, techniques which are analogous to the syntheses of known structurally similar intermediates or starting materials and the procedures described in the preparations and examples below, including any novel procedures. Such known procedures include, but are not limited to, esterification of a carboxylic acid, hydrolysis of a nitrile to a carboxylic acid, and subsequent esterification. In addition, one of ordinary skill will appreciate that many of the necessary reagents or starting materials can be readily obtained from commercial suppliers or custom synthesis groups. The R, R^1, R^2, R^3, R^4, R^5, R^6, w, x, y, z, etc, used within this section for the purpose of illustrating the various methods of synthesizing compounds of the invention are not necessarily synonymous in scope or meaning with similar groups used in the generic structure for compounds of formula I, assuming w, x, y, z do not all equal carbon. However, groups in similar positions are co-

extensive in scope and meaning compared to groups occupying similar positions as defined for the generic structure of compounds of formula **I**.

Scheme 1



Synthetic scheme 1 shows preparation of compounds of formula I wherein j is 1 and n is 0. For example, substituted heteroarylamino esters **1** that are either commercially available or prepared as set forth in the literature or in Schemes 1a to 1d can be protected with tosyl chloride, isopropyl chloroformate, or other suitable protecting group to provide **2**. The compound **2** may in turn be alkylated with appropriately substituted, or unsubstituted 3-bromopropanoic acid esters **11** thus affording **3**. Dieckmann

condensation-cyclization of intermediate **3** yields N-protected heteroarylazepine **4**, which is subjected to acid hydrolysis and decarboxylation to afford heteroarylazepin-5-one derivatives **5**. Removal of the protecting group, if necessary, with acid (e.g. PPA (polyphosphoric acid)), TMSI (trimethylsilyliodide), or HCl provides the intermediate heteroarylazepin-5-one **6**. Alternatively, utilizing the same conditions to effect **7** to **8**, one can proceed directly to **8** without deprotection.

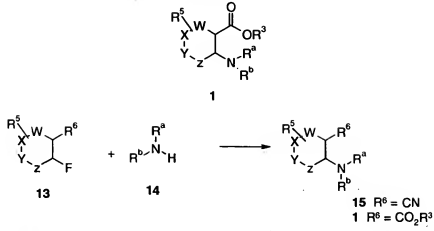
N-acylation of **6** by treatment with an appropriately substituted aryl or alkyl chloroformate in the presence of an organic base such as pyridine affords carbamates of structure **7**. Alternatively, treatment of **6** with an acid chloride or an appropriate activated ester, such as those generated *in-situ* from the reaction of an appropriately substituted aryl or alkyl carboxylic acid affords compounds of formula **7**.

Generation of urea derivatives from **6** is accomplished by treatment with a carbamoyl chloride in the presence of base such as pyridine and DMAP (dimethylamino pyridine) or an alternative base such as NaH in DMF. Alternatively, treatment with phosgene, or carbodiimide (CDI) reagent such as cyclohexylcarbodiimide or analog thereof, followed by the addition of an appropriately di-substituted amine will afford ureas of structure **7**. Formation of sulfonamide derivatives from **6** can be accomplished by reaction with appropriately substituted sulfonyl chlorides in the presence of a base.

Conversion of ketone **7** to **10** may be performed through direct reductive amination with an appropriately substituted alkylamine or aryl amine to afford compound **9**. Alternatively, compound **9** may be prepared through formation of the amine derivate **8** by reduction of an intermediate oxime, followed by alkylation with an appropriately substituted benzylic halide, mesylate or tosylate, or by reductive alkylation with the appropriate aldehyde or ketone in the presence of a reducing reagent such as $NaCNBH_3$. Compound **9** is converted to **10** (a compound of the invention) by acylation with an appropriately substituted symmetrical anhydride or acid halides to afford amides. Reaction of compound **9** with chloroformates affords the corresponding carbamates, Reaction of **9** with isocyanates, carbamoyl chlorides, or appropriately substituted sulfonyl chlorides affords the corresponding urea or sulfonamides respectively.

The intermediate compound (**1**) may be prepared as shown and described in schemes 1a through 1d below:

Scheme 1a.

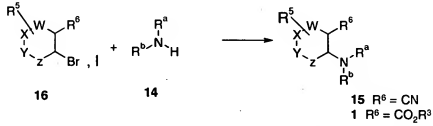


1

13 **14** **15** R^6 = CN; **1** R^6 = CO_2R^3

In scheme 1a, the nucleophilic aromatic substitution occurs by methods known in the art, (Wells, K. M. et al. Tetrahedron Letters, 1996, 37(36), 6439-6442). The appropriately substituted amine **14**, such as benzylamine, is dissolved in a suitable solvent, such as DMF or DMSO. A base such as cesium carbonate is added. The appropriately substituted fluoro heterobenzoate or heterobenzonitrile **13** (R^6 = CN or CO_2R^3), such as methyl fluoronicotinate ester is also added. The reaction proceeds at 0°C to elevated (up to about 150°C) temperatures in anywhere from ten minutes to several days depending on the stability of the starting materials. The product of structure **15** (R^6 = CN) or **1** ($R^6 = CO_2R_3$) can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

Scheme 1b

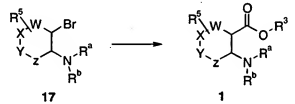


16 **14** **15** R^6 = CN; **1** R^6 = CO_2R^3

In scheme 1b, the N-Aryl coupling occurs by methods known in the art, (Hartwig, J. F. et al. Angew. Chem., Int. Ed. Engl. 1998, *37*, 2046-2067). The appropriately substituted amine **14** is dissolved in a suitable solvent, such as DMF. A base, such as cesium carbonate or sodium *tert*-butoxide, the appropriately substituted halogenated

heterobenzoate or heterobenzonitrile **16** (R^6 = CN or CO_2R^3), and a suitable catalyst complex, such as palladium acetate and diphenyl phospino ferrocene ligand are added. The reaction proceeds at 0°C to elevated temperatures (up to 150°C) in anywhere from ten minutes to several days depending on the stability of the starting materials. The product of structure **15** (R^6 = CN) or **1** (R^6 = CO_2R^3) can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

Scheme 1c



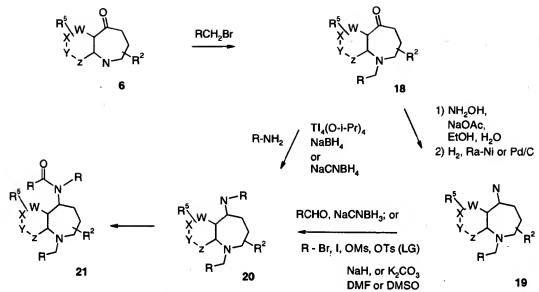
In scheme 1c, the carbonylation occurs by methods known in the art, (Heck, *Palladium Reagents in Organic Synthesis;* Academic Press: New York, 1985, p. 348-358). The appropriately substituted heteroaryl bromide **17** is dissolved in a suitable solvent, such as DMF, followed by addition of a base, such as cesium carbonate or sodium *tert*-butoxide/ A suitable catalyst complex, such as palladium acetate and diphenyl phospino ferrocene, an appropriate alcohol (R^3-OH) are added. The reaction mixture is then saturated with carbon monoxide. The reaction proceeds at 0°C to elevated temperatures (up to about 150°C) in anywhere from ten minutes to several days depending on the stability of the starting materials. The reaction may also be preformed under pressure using procedures known to one of skill in the art. The product of structure **1** may then be isolated by a standard aqueous workup, optionally followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

Scheme 1d

17 1

In scheme 1d, the aromatic carboxylation occurs by methods known in the art, (Boger, D. L. et al, Journal of Organic Chemistry, 1994, 59(17), 4943-4949, Volpin et al, *Organomet. Reactions*, 1975, *5*, 313-386). The appropriately substituted heteroaryl bromide **17** is dissolved in a suitable solvent, such as diethyl ether or tetrahydrofuran. An alkyl lithium, such as n-butyl lithium or *tert*-butyl lithium or magnesium turnings is added. The resulting anion is quenched with a suitable carbon dioxide source, such as dry ice, or dimethyl carbonate. The reaction proceeds at -78°C to room temperature in anywhere from about five minutes to several hours depending on the stability of the starting materials. The product of structure **1** can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

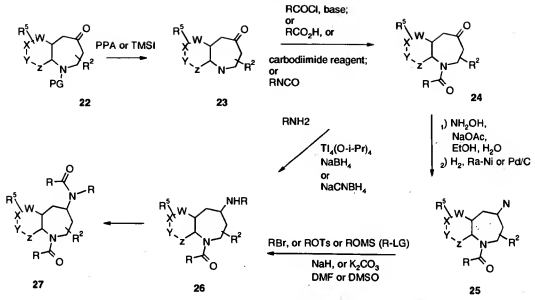
Scheme 2



In scheme 2, the ring nitrogen of compound **6** can be alkylated by methods known in the art (Tetrahedron, 2002, 58 (43), 8719-8727) such as by treating the appropriately substituted heterobenzazapine, **6**, with a base such as sodium carbonate or sodium hydride, and an alkylating agent, such as methyl bromoacetate or chloroacetonitrile, to afford the intermediate **18.** The final product **21** can then be obtained according to the procedure described in scheme 1.

Compounds of the invention wherein R^4 is hydrogen and R^3 is NR^9R^{10} may be prepared as shown below in scheme 3.

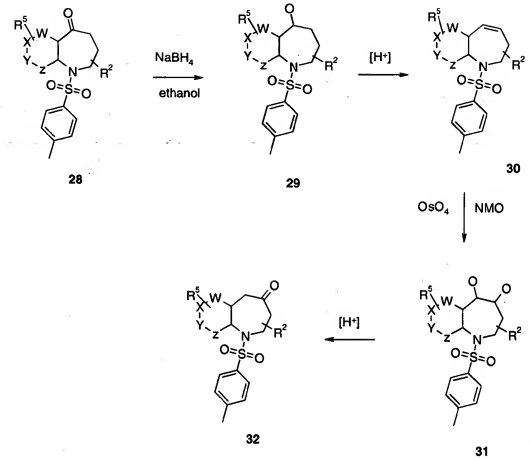
Scheme 3



As shown in scheme 3, intermediates of general structure **22** are converted to **27** (a compound of the invention) utilizing the steps similar to that described for Scheme 1.

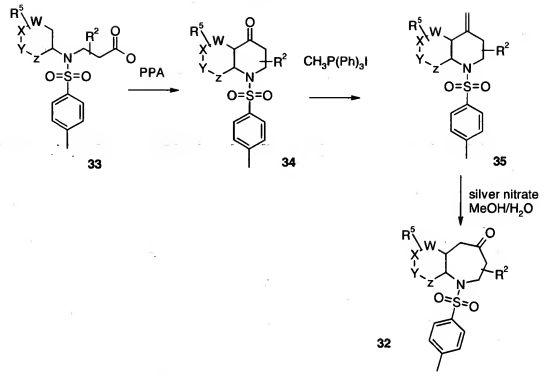
The intermediate **22** may be prepared following the reaction schemes 3a or 3b below:

Scheme 3a



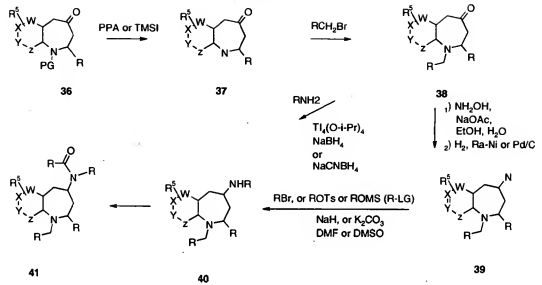
N-tosyl heterobenzazepine-5-ones of general structure **28** are converted to compounds of general structure **32** utilizing the steps outlined in Scheme 3a. Reduction of the ketone can be effected using a variety of reducing agents such as sodium borohydride to yield compound **29**. This compound can then be eliminated to the olefin via an acid catalyzed procedure known to one of ordinary skill in the art to afford **30**. The olefin can then be oxygenated to the diol **31** in a variety of ways such as the use of a catalytic amount of osmium tetroxide with N-methyl morpholine oxide (NMO). This diol can then be converted to compound **32** by treatment with an appropriate acid to eliminate the benzyl alcohol and tautomerize to the ketone. *c.f.*: Burnell, R.H., Jean, M; *Synthetic Communications*, 14(13), 1229-1237 (1984).

Scheme 3b.



Alternatively the ketones **34** and **32** may be made via Scheme 3b (Booker-Milburn, K.I., et al.; J. *Chem. Soc., Perkin Trans. 1*, 3261-3273 (1997)). N-(*p*-tolylsulfonyl)-3-aminopropanoic acids can be made by alkylation of the approprate aniline via a procedure similar to that shown in Scheme 1 and then saponification of the resulting ester to yield compound **33**. Compound **33** may then undergo an intermolecular acylation to form the 4-keto quinolin-4-one **34,** using a variety of procedures known in the art. Wittig reaction of this compound with methyltriphenylphosphonium iodide and a base, such as sodium hydride, affords the olefin **35**. Using silver nitrate, the olefin **35** can be converted to the desired ketone **32** following procedures known to one of skill in the art.

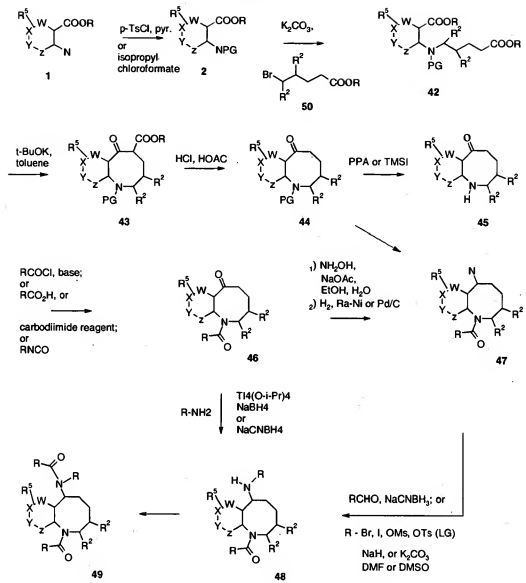
Scheme 4



In scheme 4, the nitrogen can be alkylated by methods known in the art (Tetrahedron, 2002, 58 (43), 8719-8727) such as by treating the appropriately substituted heterobenzazapine **37** with base such as sodium carbonate or sodium hydride, and an alkylating agent, such as methyl bromoacetate or chloroacetonitrile to afford the intermediate **38.** The final product **41** may be obtained according to the procedure described in Scheme 1.

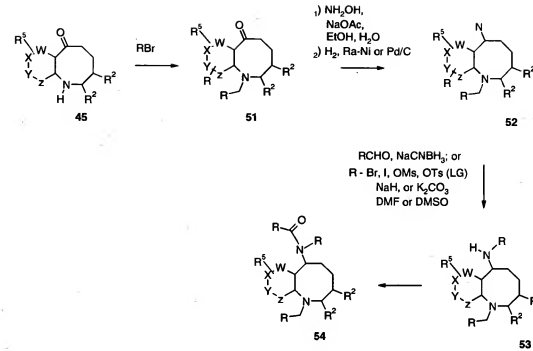
Compounds of the invention wherein j is 2, i.e. heterobenzazacines may be prepared following the procedure of scheme 5 below:

Scheme 5



Under conditions similar to those of Scheme 1, heterobenzazacine compounds of formula I (**49**) are prepared utilizing the steps outlined in Scheme 5. By using an appropriately substituted bromo propionate **50**, followed by a Dieckmann condensation-cyclization, the heterobenzazacin-ones **43** may be synthesized. Further elaboration to final products **49** proceed according to Scheme 1.

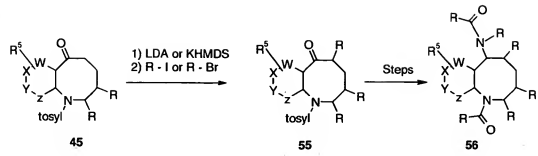
Scheme 6



In Scheme 6, the nitrogen can be alkylated by methods known in the art (Tetrahedron, 2002, 58 (43), 8719-8727) such as by treating the appropriately substituted heterobenzazapine **45**, with base and an alkylating agent, such as methyl bromoacetate or chloroacetonitrile, to afford intermediate **51.** The final product **54** may then be obtained according to the procedure described in Scheme 1.

Compounds of formula I wherein neither R^4 nor R^3 is hydrogen, and neither R^4 nor R^3 is NR^9R^{10} may be prepared as shown below in scheme 7 for j is 2.

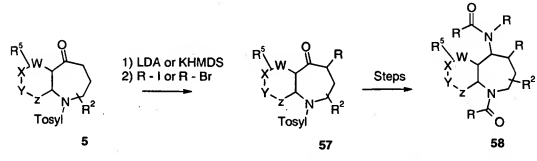
Scheme 7



Installation of substituents alpha to the carbonyl of 1-heterobenzazacin-6-one **45** can be accomplished for example according to the method outlined in scheme 7 by enolate formation followed by alkylation with an appropriate alkyl halide. Conversion of **55** to **56** is as described, for example in Scheme 1.

Compounds of formula **I** wherein neither R^4 nor R^3 is hydrogen and both R^4 and R^5 are not NR^9R^{10} may also be prepared as shown below in scheme 8 for j is 1.

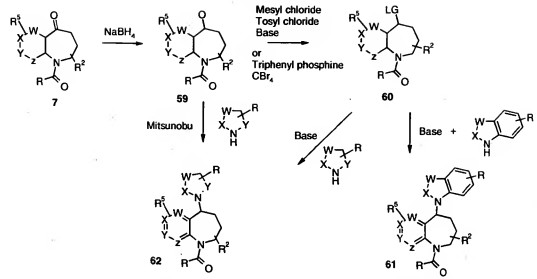
Scheme 8



Installation of substituents alpha to the carbonyl of 1-heterobenzazapin-5-one **5** can be accomplished for example according to the method outlined in scheme 8 by enolate formation followed by alkylation with an appropriate alkyl halide. Conversion of **57** to **58** is as described, for example in Scheme 1.

Compounds of formula I where p is 1, R^4 is NR^9R^{10}, and R^9 and R^{10} combine to form a monocyclic or bicyclic ring including heterocycles, may be prepared as shown in scheme 9.

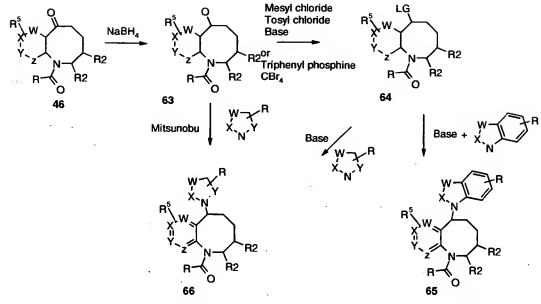
Scheme 9



Heterocyclic substituents at the 5-position of the heterobenzazapine can be prepared according to Scheme 9. The intermediate heterobenzazepin-5-one **7** described in Scheme 1 is reduced with a reducing agent such as sodium borohydride in an appropriate solvent, such as tetrahydrofuran and methanol, to achieve the alcohol **59**. Subsequent Mitsonobu chemistry known to one of ordinary skill in the art (Tetrahedron Lett 2002, 43 (12), 2187-2190) affords the product **62**. Alternatively, the carbinol **59** may be converted to a leaving group either with mesyl chloride or tosyl chloride and base, such as pyridine, or with triphenyl phosphine and carbon tetrabromide to afford **60**. Displacement of the leaving group by the either a benzofused or substituted heterocycle, utilizing a base, such as cesium carbonate or sodium hydride, affords the product **61** or **62**, respectively.

Compounds of formula I where p is 2, R^4 is NR^9R^{10}, and R^9 and R^{10} combine to form a monocyclic or bicyclic ring including heterocycles, may be prepared as shown in Scheme 10.

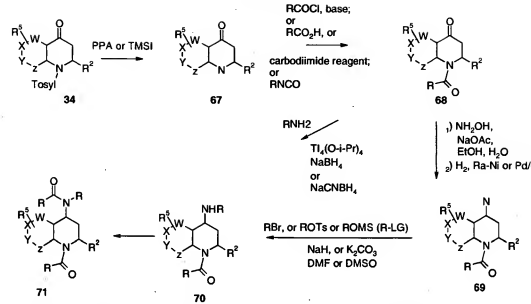
Scheme 10



According to scheme 10, heterocyclic substituents at the 6-position (R^4) of the heterobenzazacine **46** may be prepared utilizing conditions similar to those described in scheme 9, to afford products **65** and **66**.

Compounds of formula I wherein the B ring is a six-member ring may be prepared in one instance according to scheme 11 below.

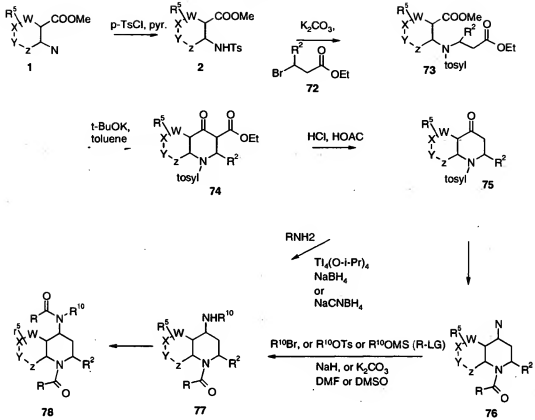
Scheme 11



As shown in Scheme 11, intermediates of general structure **34** (prepared in Scheme 3b) are converted to **71** (a compound of the invention) utilizing conditions described in Scheme 1.

Compounds of formula **I** wherein j is 0 may be also be prepared according to scheme 12 below.

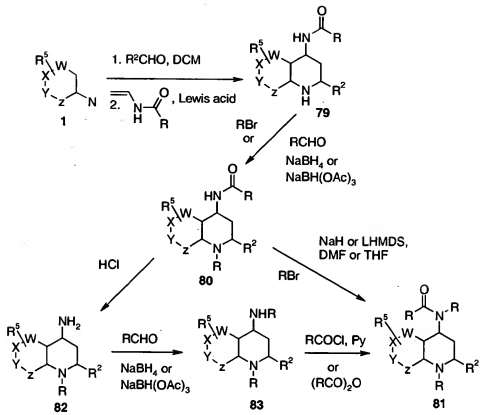
Scheme 12



As shown in Scheme 12 intermediates of general structure **1** such as for example 2-aminopyridine 3-methylcarboxylate, are converted to **78** (a compound of the invention) utilizing conditions similar to those described in Scheme 1.

Compounds of formula **78** can be prepared according to Scheme 13.

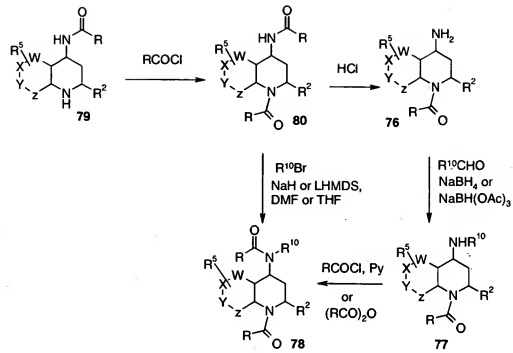
Scheme 13



As shown in Scheme 13, heteroaryl amine **1** such as for example 2-methoxy-5-aminopyridine, can be converted to **79** by reaction of the appropriate aldehyde or ketone, followed by treatment with an N-acylated enamine in the presence of acid. Reductive amination, or alkylation provides **80**, a compound of the invention, which can be further functionalized at the N-4 nitrogen by amide hydrolysis to give **82**, which in turn is alkylated via reductive amination to provide **83**. Compound **83** may be acylated or sulfonylated using standard procedures by one skilled in the art tot provide **81**. Alternatively amide 80 may be directly alkylated using an appropriate alkyl halide, alkyl tosylate, or the like, in the presence of base to provide **81**.

Alternatively, compounds of the present invention may also be prepared according to Scheme 14 or known variations thereof.

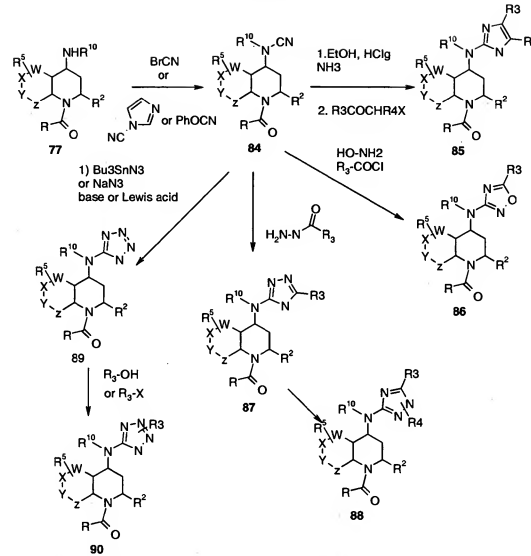
Scheme 14



Compound **79** is acylated to provide compound **80**, which in turn is selectively hydrolysed to afford amine **76**. Compound **80** can be alkylated using an appropriate alkyl halide, alkyl tosylate, or the like, in the presence of base to provide **78.** Alternatively, **76** can be alkylated using reductive amination conditions to afford **77**, which in turn may be acylated or sufonylated to afford **78**.

Certain compounds of formula I may be prepared as shown in Scheme 15.

Scheme 15



As shown in Scheme 15, amine **77** can be treated with for example cyanogen bromide or N-cyano imidazole in the presence or absence of base to form the N-cyano derivative **84**. The synthesis of imidazole **85**, tetrazole **89**, oxadiazole **86**, and triazole **87** is illustrated in the Scheme. Triazole **87** can be alkylated using an appropriate alkyl iodide, mesylate, or the like in the presence of base to afford 88. Tetrazole **89** can be alkylated using the appropriate alcohol under Mitsunobu conditions, or with the appropriate alkyl iodide, mesylate, or the like in the presence of base to provide **90**.

ASSAY

The following assay protocol and result(s) thereof demonstrating the utility and efficacy of the compounds and/or methods of the current invention are given for the purpose of illustration and are not meant to be limiting in any way.

IN VITRO CETP INHIBITOR ASSAY: SPA ASSAY

An in vitro Scintillation proximity assay (SPA) has been used to test the ability of compounds of this invention to inhibit the transfer of radiolabeled cholesterol esters between HDL and LDL. This assay monitors the inhibition of the transfer of [^{3}H]cholesterol esters from HDL (Amersham) to biotinylated LDL (Amersham) by a CETP source. CETP produced by AV-12 cells that have been created to express human CETP has been used mediate the transfer. After 30 minutes incubation in which the radiolabeled cholesterol ester is transferred in a HEPES-NaCl based buffer, the reaction is stopped and the biotinylated LDL is bound to streptavidin/scintillant coated SPA beads (Amersham). Then the radioactive signal has been measured in a Packard 96-well scintillation TopCounter with window settings fully open. A decrease in radioactive signal represents the ability of compounds of the invention to inhibit the activity of CETP.

Alternatively, additional CETP sources can be used to mediate the transfer of radiolabeled cholesterol ester in this assay. Endogenous CETP from human plasma, CETP from mice made to express human CETP, and endogenous CETP from hamsters can be used as the CETP source in this assay.

Alternatively, other sources may be used as the buffer. In addition to the HEPES-NaCl based buffer that has been used in this assay, human plasma, mouse plasma or a Tris-bufer that is high in albumin may be used as the buffer in which the transfer of radiolabeled cholesterol esters from HDL to LDL may occur.

Alternatively, other sources of radioactivity may be used to track the CETP activity in this assay. In yet another alternative, radiolabeled-LDL may be used in this assay.

Compounds of the present invention tested have shown inhibition of CETP activity below about 100 micromolar when subjected to the SPA assay procedure above.

ASSAY OF CETP ACTIVITY *IN VIVO*.

Syrian Golden Hamsters, which express endogenous CETP, are used to assess the activity of the compounds *in vivo*. Test compounds are administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood can be obtained. CETP activity is determined by a method similar to that described for the *in vitro* CETP activity assay, except that plasma from treated animals is used as the CETP source in the assay.

A strain of transgenic mice that express human CETP (Taconic, Germantown, NY) are used to test compounds of this invention. Test compounds are administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood can be obtained. CETP activity is determined by a method similar to that described for the *in vitro* CETP activity assay, except that plasma from treated animals is used as the CETP source in the assay.

Alternatively, a strain of transgenic mice that express both human CETP and human apolipoprotein A-1 (Taconic, Germantown, NY) are used to test compounds of this invention. Test compounds are administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood is obtained. CETP activity is determined by a method similar to that described for the *in vitro* CETP activity assay, except that plasma from treated animals is used as the CETP source in the assay.

ASSAY OF PLASMA LIPIDS *IN VIVO*.

The efficacy of these compounds *in vivo* can also be determined utilizing Syrian Golden Hamsters. The compounds can be tested in hamsters made hypercholesterolemic by feeding a high fat high cholesterol diet for a minimum of two weeks or in non-hypercholesterolemic hamsters fed normal chow for two weeks. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum can be obtained and lipids can be analyzed by enzymatic methods. Lipids in the VLDL, LDL and HDL fractions are analyzed by enzymatic methods after precipitation or size exclusion chromatography.

Alternatively, a strain of transgenic mice that express human CETP (Taconic, Germantown, NY) are used to test the efficacy of the compounds of this invention. The hCETP mice can be made hypercholesterolemic by feeding a high fat chow diet such as

TD 88051, as described by Nishina et al. (J Lipid Res., 31, 859-869 (1990)) for at least two weeks before the start of the study. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum can be obtained and lipids can be analyzed by enzymatic methods. Lipids in the VLDL, LDL and HDL fractions are analyzed by enzymatic methods after precipitation or size exclusion chromatography.

Alternatively, a strain of transgenic mice that express both human CETP and human apolipoprotein A-1 (Taconic, Germantown, NY) are used to test the efficacy of the compounds of this invention. The mice that express both human CETP and human apolipoprotein A1 can be made hypercholesterolemic by feeding a high fat chow diet such as TD 88051, as described by Nishina et al. (J Lipid Res., 31, 859-869 (1990)) for at least two weeks before the start of the study. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum can be obtained and lipids can be analyzed by enzymatic methods. Lipids in the VLDL, LDL and HDL fractions can be analyzed by enzymatic methods after precipitation or size exclusion chromatography.

Method of Treatment

As used herein, the term "effective amount" means an amount of compound of the present invention, i.e., formula I, which is capable of alleviating the symptoms of the various pathological conditions herein described. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level of from about 0.01 mg to about 100 mg/day of a compound of the present invention. Preferred daily doses generally will be from about 1 mg to about 250 mg/day.

The compounds of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician. Thus, another aspect of the present invention is a pharmaceutical composition comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, solvate, prodrug,

enantiomer or prodrug thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients and salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Pharmaceutical formulations of the present invention can be prepared by procedures known in the art using well-known and readily available ingredients. For example, the compounds of formula I can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds also can be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular physiological location, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

Compounds of formula I, generally, will be administered in a convenient formulation as determined by the attending physician. The following formulation examples are only illustrative and are not intended to limit the scope of the present invention.

Formulations

In the formulations which follow, "Active Ingredient" means a compound of formula I, a salt, solvate, racemate, enantiomer diastereomer or mixture of diastereomers, or prodrug thereof, or a combination of a compound of formula I and other effective agent for the treatment or prevention of dyslipidemia or atherosclerosis.

Formulation 1:Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The formulation above may be changed in compliance with the reasonable variations provided.

A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	2.5 - 1000
Cellulose, microcrystalline	200 - 650
Silicon dioxide, fumed	10 - 650
Stearate acid	5 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 2.5 - 1000 mg of active ingredient are made up as follows:

Formulation 3: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	25 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders that are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules, which after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 ml dose are made as follows:

Formulation 4: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30° C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Formulation 6: Intravenous Solution

Ingredient	Quantity
Active ingredient	50 mg
Isotonic saline	1,000 mL

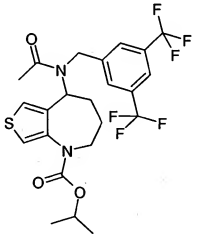
The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

Examples

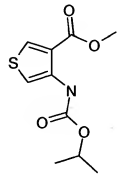
The following examples are illustrative of compounds made or compounds that could be made by one of skill in the art following the teachings disclosed herein and known to one of skill in the art and requiring minimal experimentation. The disclosed examples should in no way limit the scope of the claims.

Example 1

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester

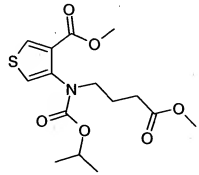


Step 1. Preparation of 4-Isopropoxycarbonylamino-thiophene-3-carboxylic acid methyl ester



Pour 2.0N $NaOH_{(aq)}$ (100 ml) into a mixture of methyl 3-aminothiophene-4-carboxylate hydrochloride (3.26 g, 16.8 mmol) and isopropyl chloroformate (1.0N in toluene, 50.5 ml) in dichloromethane (100 ml). Stir the reaction mixture at room temperature for 4 hours. Adjust pH = 2~4 by adding 1.0N HCl. After layer separation, extract the aqueous layer with dichloromethane (100 ml). Wash the combined organic phases with brine (3 x 200 ml), then dry over Na_2SO_4. Filter and concentrate. Purification by silica gel column (gradient eluent, 0-20% ethyl acetate in hexane) provides 4-Isopropoxycarbonylamino-thiophene-3-carboxylic acid methyl ester (3.15 g, 77%) as an oil. MS (ES+): 244 (M+H).

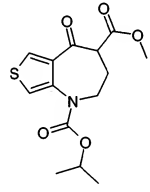
Step 2. Preparation of 4-[Isopropoxycarbonyl-(3-methoxycarbonyl-propyl)-amino]-thiophene-3-carboxylic acid methyl ester



Suspend NaH (60% in mineral oil, 0.508 g, 12.7 mmol) in anhydrous DMF (50 ml) and cool the mixture to 0°C. Inject a solution of 4-Isopropoxycarbonylamino-thiophene-3-carboxylic acid methyl ester (3.10 g, 12.7 mmol) in DMF (50 ml) dropwise and then

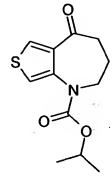
warm up the mixture to room temperature for an hour. Add methyl 4-bromobutyrate (3.57 g, 19.1 mmol), and then stir for 4 hours at room temperature. Dilute the reaction mixture with 200 ml ethyl acetate, wash with $HCl_{(aq)}$ (1 x 200 ml). Extract aqueous with more ethyl acetate (100 ml). Combine the organic layers, wash with brine (3 x 300 ml). Dry over Na_2SO_4 and concentrate. Purification by silica gel column (gradient eluent, 0-20% ethyl acetate in hexane) provides 4-[Isopropoxycarbonyl-(3-methoxycarbonyl-propyl)-amino]-thiophene-3-carboxylic acid methyl ester (2.38 g, 55%) as an oil. MS (ES+): 344 (M+H).

Step 3. Preparation of 5-Oxo-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1,4-dicarboxylic acid 1-isopropyl ester 4-methyl ester



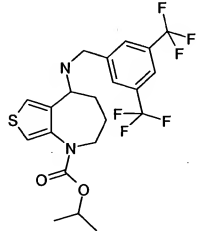
Inject a solution of 4-[Isopropoxycarbonyl-(3-methoxycarbonyl-propyl)-amino]-thiophene-3-carboxylic acid methyl ester (2.30 g, 6.70 mmol) in toluene (100 ml) dropwise to a preheated solution of potassium t-butoxide (1.53 g, 13.4 mmol) in toluene (100 ml) at 70°C. After finish the addition, cool the mixture down to room temperature. Pour the reaction mixture into ice-water (100 ml) and adjust pH by adding 1N HCl (15 ml). Separate the organic layer and extract aqueous with ethyl acetate (2 x 100 ml). Combine the organic layers, and then wash with brine (3 x 300 ml). Dry over Na_2SO_4, filter and evaporate the solvents on a rotary evaporator (rota-vapor). Purification by silica gel column (gradient eluent, 0-10% ethyl acetate in hexane) to give 5-Oxo-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1,4-dicarboxylic acid 1-isopropyl ester 4-methyl ester (1.68 g, 80%) as an oil. MS (ES+): 312 (M+H); (ES-): 310 (M-H).

Step 4. Preparation of 5-Oxo-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester



Add LiCl (0.300 g, 7.18 mmol) in one portion to a mixture of 5-Oxo-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1,4-dicarboxylic acid 1-isopropyl ester 4-methyl ester (0.930 g, 2.99 mmol) in DMSO (24 ml) and H_2O (2 drops). Heat the mixture at 160°C for 2 hours. Cool down to room temperature, partition between ethyl acetate (50 ml) and brine (50 ml). Separate the organic layer, wash with brine (3 x 50 ml). Dry over Na_2SO_4 and concentrate to an oil. Purification by silica gel column (gradient eluent, 0-15% EtOAc in hexane) to give 5-Oxo-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester (0.272 g, 36%) as an oil. MS (ES+): 254 (M+H).

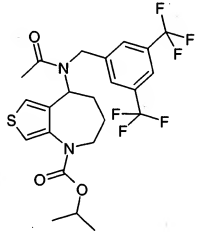
Step 5. Preparation of 5-(3,5-Bis-trifluoromethyl-benzylamino)-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester



Inject titanium(IV)isopropoxide (0.390 ml, 1.33 mmol) to a mixture of 5-Oxo-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester (0.269 g, 1.06 mmol),

3,5-Bis(trifluoromethyl)benzylamine (0.258 g, 1.06 mmol), and then stir at room temperature for 16 hours. Inject a solution of $NaCNBH_3$ (0.266 g, 4.24 mmol) in methanol (10 ml) to the reaction mixture and continue to stir at room temperature overnight. Treat the mixture with 0.1 N NaOH (25 ml) for 10 minutes, and then filter through a Celite pad. Wash the filtered residue thoroughly with ethyl acetate. Separate the organic layer, wash with brine (3 x 50 ml), dry over Na_2SO_4 and concentrate to provide crude 5-(3,5-Bis-trifluoromethyl-benzylamino)-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester (0.518 g) which was elaborated without further purification. MS (ES+): 481 (M+H).

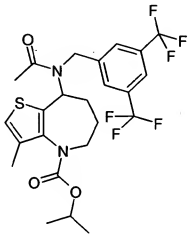
Step 6. Preparation of 5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester



Inject acetic anhydride (0.40 ml, 4.24 mmol) dropwise to a solution of crude 5-(3,5-Bis-trifluoromethyl-benzylamino)-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester (0.277 g, 0.577 mmol) and pyridine (0.40 ml, 4.96 mmol) in dichloromethane (4 ml) at room temperature. Stir the mixture at room temperature for 16 hours. Dilute the reaction mixture with 50 ml ethyl acetate, and then wash with $HCl_{(aq)}$ (1 x 50 ml) and brine (3 x 50 ml). Dry over Na_2SO_4 and concentrate to an oil. Purification by silica gel column (gradient eluent, 0-30% ethyl acetate in hexane) provides the title compound (230 mg, white crystalline). MS (ES+): 523 (M+H).

Example 2

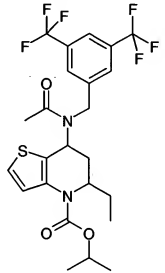
8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3-methyl-5,6,7,8-tetrahydro-thieno[3,2-b]azepine-4-carboxylic acid isopropyl ester



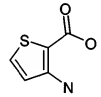
Following the procedures described in **Example 1** by replacing methyl 3-aminothiophene-4-carboxylate hydrochloride (**Example 1**, step 1) with methyl 3-amino-4-methylthiophene-2-carboxylate gives the title compound. MS (ES+): 537 (M+H).

Example 3

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5-ethyl-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester

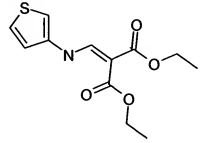


Step 1. Preparation of 3-Amino-thiophene-2-carboxylic acid



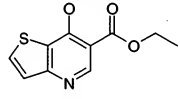
Add $NaOH_{(aq)}$ (5.0N, 50 ml) to a solution of methyl 3-aminothiophene-2-carboxylate (7.86, 50.0 mmole) in MeOH (250 ml). Heat the reaction mixture at 60°C overnight. Adjust pH = 6~7 by adding 1.0N HCl. Extract with ethyl acetate (5x200 ml). Combine organic layers, dry over Na_2SO_4. Filter and concentrate to provide 3-Amino-thiophene-2-carboxylic acid (5.84 g, 82%) as white powder, which was used immediately for the next step. MS (ES+): 144 (M+H); (ES+): 142 (M-H).

Step 2. Preparation of 2-(Thiophen-3-ylaminomethylene)-malonic acid diethyl ester



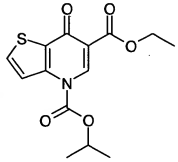
Add diethyl ethoxymethylenemalonate (8.99 ml, 44.9 mmol) to a solution of 3-Amino-thiophene-2-carboxylic acid (5.84 g, 40.8 mmol) in toluene (100 ml). Heat the mixture under reflux overnight. Evaporate the solvent on a rota-vapor. Purification by silica gel column (gradient eluent, 0-20% ethyl acetate in hexane) provides 2-(Thiophen-3-ylaminomethylene)-malonic acid diethyl ester (7.86 g, 86%) as white crystalline. MS (ES+): 270 (M+H).

Step 3. Preparation of 7-Hydroxy-thieno[3,2-b]pyridine-6-carboxylic acid ethyl ester



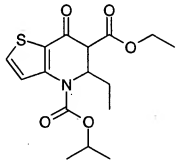
Add 2-(Thiophen-3-ylaminomethylene)-malonic acid diethyl ester (7.66 g, 28.4 mmol) to the refluxing phenyl ether (100 ml) over a period of 5 minutes under nitrogen. After finish the addition, keep the reaction under reflux for 30 minutes. Cool it to room temperature, and then pour the reaction mixture into ethyl acetate (1000 ml). Collect the brown precipitation by filtration to obtain 7-Hydroxy-thieno[3,2-b]pyridine-6-carboxylic acid ethyl ester (4.82 g, 76%). MS (ES+): 224 (M+H); (ES-): 222 (M-H).

Step 4. Preparation of 7-Oxo-7*H*-thieno[3,2-b]pyridine-4,6-dicarboxylic acid 6-ethyl ester 4-isopropyl ester



Add pyridine (1.20 ml, 14.8 mmol) to a suspension of 7-Hydroxy-thieno[3,2-b]pyridine-6-carboxylic acid ethyl ester (1.10 g, 4.93 mmol) in DCM (50 ml), and then add isopropyl chloroformate (1.0N in toluene, 14.8 ml). Stir the reaction mixture at room temperature overnight. Wash the mixture with 1.0N HCl (50 ml) followed by brine (3x50 ml). Separate the organic layer, dry over Na_2SO_4. Filter and concentrate. Purification by silica gel column (gradient eluent, 0-60% ethyl acetate in hexane) provides 7-Oxo-7*H*-thieno[3,2-b]pyridine-4,6-dicarboxylic acid 6-ethyl ester 4-isopropyl ester (1.37 g, 90%) as white crystalline. MS (ES+): 310 (M+H).

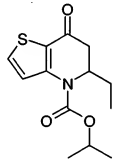
Step 5. Preparation of 5-Ethyl-7-oxo-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4,6-dicarboxylic acid 6-ethyl ester 4-isopropyl ester



Mix 7-Oxo-7*H*-thieno[3,2-b]pyridine-4,6-dicarboxylic acid 6-ethyl ester 4-isopropyl ester (0.512 g, 1.66 mmol) and copper(I) iodide (0.695g, 3.65 mmol) in THF (35 ml). Cool the mixture to –78°C. Inject ethyl magnesium bromide (3.0M in diethyl ether, 1.66 ml) and stir for 1.5 hours. Add another portion of ethyl magnesium bromide (3.0M in diethyl ether, 3.30 ml) and keep the reaction at –78°C for one more hour. Warm up to –20°C

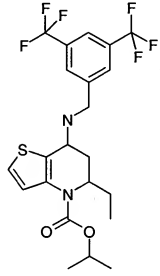
overnight in frizer. Pour the reaction mixture into saturated $NH_4Cl_{(aq)}$ (200 ml). Extract with ethyl acetate (3x200 ml). Combine all the organic layers, dry over Na_2SO_4 and concentrate to give 5-Ethyl-7-oxo-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4,6-dicarboxylic acid 6-ethyl ester 4-isopropyl ester (0.520 g, 93%) as crude oil. MS (ES+): 340 (M+H).

Step 6. Preparation of 5-Ethyl-7-oxo-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester



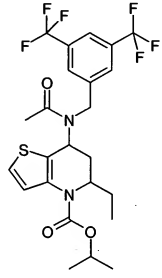
Add LiCl (0.162 g, 3.83 mmol) in one portion to a mixture of 5-Ethyl-7-oxo-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4,6-dicarboxylic acid 6-ethyl ester 4-isopropyl ester (0.520 g, 1.53 mmol) in DMSO (15 ml) and H_2O (2 drops). Heat the mixture at 160°C for 4 hours. Cool down to room temperature, partition between ethyl acetate (50 ml) and brine (50 ml). Separate the organic layer, wash with brine (3 x 50 ml). Dry over Na_2SO_4 and concentrate. Purification by silica gel column (gradient eluent, 0-15% EtOAc in hexane) to give 5-Ethyl-7-oxo-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester (0.236 g, 58% for two steps) as an oil. MS (ES+): 268 (M+H).

Step 7. Preparation of 7-(3,5-Bis-trifluoromethyl-benzylamino)-5-ethyl-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester



Inject titanium(IV)isopropoxide (0.372 ml, 1.26 mmol) to a mixture of 5-Ethyl-7-oxo-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester (0.225 g, 0.842 mmol), 3,5-Bis(trifluoromethyl)benzylamine (0.211 g, 0.842 mmol), and then stir at room temperature for 4 hours. Inject a solution of $NaCNBH_3$ (0.212 g, 3.37 mmol) in methanol (8 ml) to the reaction mixture and continue to stir at room temperature overnight. Add another portion of solution of $NaCNBH_3$ (0.212 g, 3.37 mmol) in methanol (8 ml) and continue to stir for 4 hours. Add $NaBH_4$ (0.159 g, 4.21 mmol) and heat the reaction at 60oC overnight. Treat the mixture with 0.1 N NaOH (25 ml) for 10 minutes, and then filter through a Celite pad. Wash the filtered residue thoroughly with ethyl acetate. Separate the organic layer, wash with brine (3 x 50 ml), dry over Na_2SO_4 and concentrate to provide crude 7-(3,5-Bis-trifluoromethyl-benzylamino)-5-ethyl-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester (0.315 g) which was elaborated without further purification. MS (ES+): 495 (M+H).

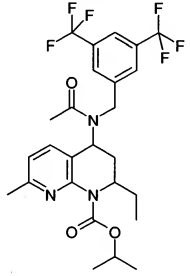
Step 8. Preparation of 7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5-ethyl-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester



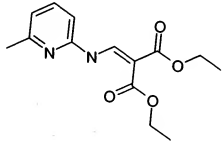
Inject acetic anhydride (0.25 ml, 2.65 mmol) dropwise to a solution of crude 7-(3,5-Bis-trifluoromethyl-benzylamino)-5-ethyl-6,7-dihydro-5*H*-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester (0.120 g, 0.243 mmol) and pyridine (0.25 ml, 3.10 mmol) in dichloromethane (1 ml) at room temperature. Stir the mixture at room temperature for 16 hours. Evaporate the solvents. Purification by silica gel column (gradient eluent, 0-35% ethyl acetate in hexane) provides the title compound (29 mg, 22%). MS (ES+): 559 (M+Na); (ES-): 535 (M-H).

Example 4

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-methyl-3,4-dihydro-2*H*-[1,8]naphthyridine-1-carboxylic acid isopropyl ester

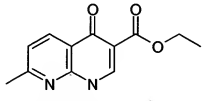


Step 1. Preparation of 2-[(6-Methyl-pyridin-2-ylamino)-methylene]-malonic acid diethyl ester



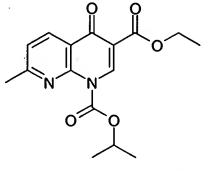
Add diethyl ethoxymethylenemalonate (10.0 ml, 55.0 mmol) to a solution of 6-Methyl-pyridin-2-ylamine (5.41 g, 50.0 mmol) in toluene (100 ml). Heat the mixture under reflux overnight. Evaporate the solvent on a rota-vapor to provide 2-[(6-Methyl-pyridin-2-ylamino)-methylene]-malonic acid diethyl ester (14.8 g) as white solid. MS (ES+): 279 (M+H).

Step 2. Preparation of 7-Methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester



Add 2-[(6-Methyl-pyridin-2-ylamino)-methylene]-malonic acid diethyl ester (14.8 g) to the refluxing phenyl ether (100 ml) over a period of 5 minutes under nitrogen. After finish the addition, keep the reaction under reflux for 3 hours. Cool it to room temperature, and then pour the reaction mixture into 1:1 hexane/ethyl acetate (2000 ml). Collect the brown precipitation by filtration to obtain 7-Methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester (8.35 g, 72% for two steps). MS (ES+): 233 (M+H); (ES-): 231 (M-H).

Step 3. Preparation of 7-Methyl-4-oxo-4H-[1,8]naphthyridine-1,3-dicarboxylic acid 3-ethyl ester 1-isopropyl ester



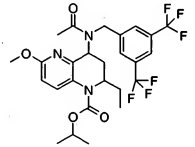
Add pyridine (2.43 ml, 30.0 mmol) to a suspension of 7-Methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester (2.32 g, 10.0 mmol) in DCM (100 ml), and then add isopropyl chloroformate (1.0N in toluene, 30.0 ml). Stir the reaction mixture at room temperature overnight. Wash eith brine (3x100 ml). Separate the organic layer, dry over Na_2SO_4. Filter and concentrate.

Steps to final product:

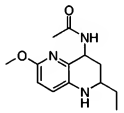
Reductive-amination on the cyclic ketone followed by alkylation on the resulting amine provides the resulting compound of formula I. Procedures for effecting reductive amination and alkylation of amines are known to one of skill in the art and/or may be derived from the synthetic schemes and/or other disclosures herein.

Example 5

Synthesis of Cis-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester.



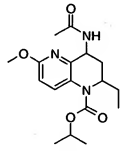
Step 1. Preparation of Cis-*N*-(2-Ethyl-6-methoxy-1,2,3,4-tetrahydro-[1,5]naphthyridin-4-yl)acetamide.



Dissolve 5-aminopyridine-2-methoxy (1.05 g, 8.05 mmol) in anhydrous dichloromethane (35 mL), add sodium sulfate (1.14 g) and cool the reaction mixture to –20 °C. Add propionaldehyde (0.659 mL, 8.85 mmol) and stir the mixture from –20 to 0 °C for 1.5 h. Filter off the sodium sulfate and add *N*-vinyl acetamide (0.706 g, 85.11 mmol) to the filtrate at –20 °C followed by boron trifluoride diethyl etherate (0.088 mL, 0.805 mmol). Stir the reaction mixture from –20 to -10 °C for 2h. Remove the solvent under vacuo and chromatograph the residue over silica cartridge, eluting with hexanes/ethyl acetate to afford the title compound (1.25 g, 63%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 7.5 Hz, 3H), 1.32 (c, J = 1.8 Hz, 1H), 1.44-1.55 (m, 2H), 2.03 (s, 3H), 2.68-2.73 (m, 1H),

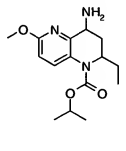
3.29-3.42 (m, 2H), 3.79 (s, 3H), 4.84-4.89 (m, 1H), 6.45-6.46 (m, 2H), 6.75 (d, J = 8.5 Hz, 1H). MS (ES+): 250 (M+H).

Step 2. Preparation of Cis-4-acetylamino-2-ethyl-6-methoxy-3,4-dihydro-2*H*-[1,5]naphthyridine-1-carboxylic acid isopropyl ester.



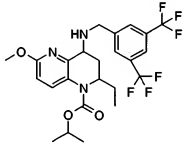
Add isopropyl chloroformate (3.10 mL, 2.82 mmol, 1.0 M in toluene) dropwise to a solution of cis-*N*-(2-Ethyl-6-methoxy-1,2,3,4-tetrahydro-[1,5]naphthyridin-4-yl)acetamide (702 mg, 3.102 mmol) and pyridine (0.677 mL, 8.46 mmol) in dichloromethane (15 mL) at 0°C under an atmosphere of nitrogen and stir at room temperature for 10 minutes. Add 1M HCl and separate the layers. Extract the aqueous layer with dichloromethane. Dry the organic layers over anhydrous sodium sulfate, filter, and remove the solvent under reduced pressure, to afford the title compound (895 mg, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J = 7.4 Hz, 3H), 1.11-1.27 (m, 7H), 1.36-1.43 (m, 1H), 1.61-1.68 (m, 1H), 2.08 (s, 3H), 2.96-3.02 (m, 1H), 3.92 (s, 3H), 4.31-4.39 (m, 1H), 4.62-4.67 (m, 1H), 4.94-4.99 (m, 1H), 6.63 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 4.0 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H). MS (ES+): 336 (M+H).

Step 3. Preparation of Cis-4-amino-2-ethyl-6-methoxy-3,4-dihydro-2*H*-[1,5]naphthyridine-1-carboxylic acid isopropyl ester.



Heat at 80 °C a solution of cis-4-acetylamino-2-ethyl-6-methoxy-3,4-dihydro-2*H*-[1,5]naphthyridine-1-carboxylic acid isopropyl ester (100 mg, 0.298 mmol) in 5N HCl (1 mL) for 4 h. Cool the reaction mixture to room temperature, pour the crude onto a saturated solution of sodium carbonate and extract with dichloromethane. Dry the organic layer over anhydrous sodium sulfate, filter, and remove the solvent under reduced pressure, to afford the title compound (85 mg, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, *J* = 7.4 Hz, 3H), 1.22 (dd, *J* = 22.6, 5.9 Hz, 6H), 1.34-1.49 (m, 2H), 1.50-1.57 (m, 1H), 1.58 (br s, 2H), 1.50-1.63 (m, 1H), 2.14 (br s, 1H), 2.46-2.52 (m, 1H), 3.85 (br s, 1H), 3.89 (s, 3H), 4.26-4.28 (m, 1H), 4.91-4.97 (m, 1H), 6.55 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H). MS (ES+): 277 (M- NH_2).

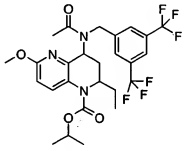
Step 4. Preparation of Cis-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-methoxy-3,4-dihydro-2*H*- [1,5]naphthyridine-1-carboxylic acid isopropyl ester.



Add sodium triacetoxyborohydride (0.091 mg, 0.409 mmol) to a mixture of 3,5-bis(trifluoromethyl)benzaldehyde (0.045 mL, 0.273 mmol), acetic acid (0.018 mL, 0.303 mmol) and cis-4-amino-2-ethyl-6-methoxy-3,4-dihydro-2*H*- [1,5]naphthyridine-1-carboxylic acid isopropyl ester (0.08 mg, 0.273 mmol) in dichloroethane (3 mL). Stir the mixture at room temperature under an atmosphere of nitrogen for 14 h. Add a saturated solution of ammonium chloride, separate layers and extract the aqueous layer with dichloromethane. Dry the combined organic layers over anhydrous sodium sulfate, filter and remove the solvent under reduced pressure. Purify the residue by flash chromatography, eluting with hexanes/ethyl acetate, to afford the title compound (125 mg, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, *J* = 7.5 Hz, 3H), 1.22 (dd, *J* = 21.3, 6.3 Hz, 6H), 1.31-1.51 (m, 2H), 1.60-1.69 (m, 1H), 2.43-2.49 (m, 1H), 3.59-3.86 (m, 1H),

3.89 (s, 3H), 4.07 (d, J = 8.3 Hz, 1H), 4.19 (d, J = 8.5 Hz, 1H), 4.26-4.33 (m, 1H), 4.78-5.27 (m, 1H), 6.60 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.75-7.89 (m, 3H). MS (ES+): 520 (M+H).

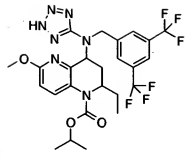
Step 5. Preparation of cis-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester.



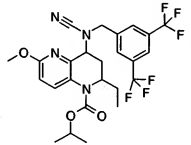
Add acetic anhydride (0.023 mL, 1.205 mmol) to a solution of cis-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-methoxy-3,4-dihydro-2*H*- [1,5]naphthyridine-1-carboxylic acid isopropyl ester (125 mg, 0.241 mmol) and pyridine (0.097 mL, 1.205 mmol) in dichloromethane (2 mL), stir at room temperature for 14h. Remove the solvent under reduced pressure and purify the residue by flash chromatography, eluting with hexanes/ethyl acetate, to afford the title compound (105 mg, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.66-0.72 (m, 3H), 1.20-1.29 (m, 7H), 1.33-1.69 (m, 3H), 2.01-2.21 (m, 3H), 2.26-2.33 (m, 1H), 3.82, 3.86 (s, 3H), 4.22-4.28 (m, 1H), 4.81-5.01 (m, 2H), 6.59, 6.65 (d, J = 8.7 Hz, 1H), 7.61-7.73 (m, 4H). MS (ES+): 562 (M+H).

Example 6

Synthesis of cis-4-[(3,5-bis-trifluoromethyl-benzyl)-(2*H*-tetrazol-5-yl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester.

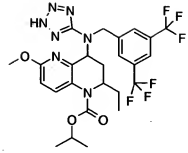


Step 1. Preparation of cis-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-cyano-amino]-2-ethyl-6-methoxy-3,4-dihydro-2*H*-[1,5]naphthyridine-1-carboxylic acid isopropyl ester.



Add diisopropylethylamine (0.146 mL, 0.962 mmol) followed by cyanogen bromide (63 mg, 0.577 mmol) to a solution of cis-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-methoxy-3,4-dihydro-2*H*- [1,5]naphthyridine-1-carboxylic acid isopropyl ester (200 mg, 0.385 mmol) in dry tetrahydrofuran (5 mL) and stir the mixture at room temperature for 15 h. Add water, separate layers and extract the aqueous layer with ethyl acetate. Dry the combined organic layers over anhydrous sodium sulfate, filter and remove the solvent under reduced pressure. Purify the residue by flash chromatography, eluting with hexanes/ethyl acetate, to afford the title compound (104 mg, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J = 7.9 Hz, 3H), 1.23 (dd, J = 22.1, 6.3 Hz, 6H), 1.44-1.51 (m, 1H), 1.62-1.79 (m, 1H), 1.81-1.87 (m, 1H), 2.61-2.68 (m, 1H), 3.86 (dd, J = 11.4, 4.8 Hz, 1H), 4.01 (s, 3H), 4.30-4.37 (m, 1H), 4.61 (d, J = 15.2 Hz, 1H), 4.82 (d, J = 14.7 Hz, 1H), 4.93-4.99 (m, 1H), 6.70 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.77-7.88 (m, 3H). MS (ES+): 545 (M+H).

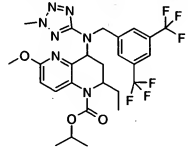
Step 2. Preparation of cis-4-[(3,5-bis-trifluoromethyl-benzyl)-(2*H*-tetrazol-5-yl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester.



Heat at 120 °C a mixture of cis-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-cyano-amino]-2-ethyl-6-methoxy-3,4-dihydro-2*H*-[1,5]naphthyridine-1-carboxylic acid isopropyl ester (100 mg, 0.184 mmol), sodium azide (17 mg, 0.258 mmol) and triethyl amine hydrochloride (35 mg, 0.258 mmol) in dry toluene under an atmosphere of nitrogen for 8 h. Add sodium azide (6 mg, 0.09 mmol) and triethyl amine hydrochloride (13 mg, 0.09 mmol) again and mantaing the heating for 4 h more. Cool the reaction mixture to room temperature, dilute with ethyl acetate and wash with 1H HCl. Separate organic layer and dry over anhydrous sodium sulfate, filter and evaporate the solvent under reduced pressure. Purify the residue by silica gel eluting with ethyl acetate/hexanes to afford the title compound (61 mg, 57%). MS (ES+): 588 (M+H).

Example 7

Synthesis of Cis-4-[(3,5-bis-trifluoromethyl-benzyl)-(2-methyl-2*H*-tetrazol-5-yl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester.

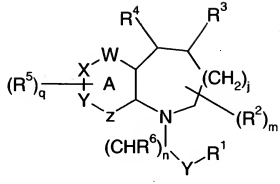


Add diethyl azodicarboxylate (0.015 mL, 0.082 mmol) to a solution of cis-4-[(3,5-bis-trifluoromethyl-benzyl)-(2*H*-tetrazol-5-yl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2*H*-[1,5]naphthyridine-1-carboxylic acid isopropyl ester (61 mg, 0.104 mmol), triphenyl phosphine (27 mg, 0.104 mmol) and methanol (0.017 mL, 0.52 mmol) in dichloromethane (1 mL) at room temperature and stir the reaction mixture for 15h. Remove the solvents under reduced pressure and purify the residue by flash

chromatography, eluting with hexanes/ethyl acetate to afford the title compound (41 mg, 66%): MS (ES+): 602 (M+H).

We claim:

1. A compound of formula I



wherein

n is 0, 1, 2, or 3;

m is 0, 1, 2, 3, 4, 5 or 6;

j is 0, 1, or 2;

q is 0, 1, or 2;

W, X, Y and Z are each independently CH, C, N, S, or O with appropriate single or double bonds and/or hydrogen atoms to complete valency requirements;

Ring A is a five or six member ring wherein one of W, X, Y or Z may be absent; provided that ring A is not phenyl;

Y is a bond, C=O, or $S(O)_p$;

p is 0, 1 or 2;

R^1 is selected from a group consisting of hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, C_1-C_6 alkylheterocyclic, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl; C_1-C_6 alkylaryl, aryl, heterocyclyl, C_2-C_6 alkylalcohol, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -OC_1-C_6 alkylheterocyclic, -OC_3-C_8 cycloalkyl, -OC_1-C_6 alkylcycloalkyl, -NR^7R^8, -OC_1-C_6 alkylaryl, -O-heterocyclic, $CONR^{11}R^{12}$, $NR^{11}SO_2R^{12}$, $NR^{11}COR^{12}$, C_0-C_3 $alkylNR^{11}R^{12}$, C_1-C_3 $alkylCOR^{11}$, C_0-C_6 $alkylCOOR^{11}$ and -OC_1-C_6 alkylheterocyclic; provided that R^1 is not hydroxy when Y is $S(O)_p$, CO, or when n and y are both zero; and wherein each cycloalkyl, aryl or heterocyclic group is optionally substituted with 1 to 3 groups independently selected from oxo, hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy,

$CONR^{11}R^{12}$, $NR^{11}SO_2R^{12}$, $NR^{11}COR^{12}$, C_0-C_3 alkyl$NR^{11}R^{12}$, C_1-C_3 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, cyano, C_1-C_6 alkylcycloalkyl, phenyl, -OC_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylaryl, -OC_1-C_6 alkylheterocyclic, and C_1-C_6 alkylaryl;

R^2 is independently selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OC_1-C_6 alkyl, C_1-C_6 alkylaryl, aryl, C_0-C_6 alkylNR^7R^8, heteroaryl, heterocyclyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl and C_1-C_6 alkylheterocyclyl; wherein each cycloalkyl, aryl, or heterocyclic is optionally substituted with 1 to 3 groups independently selected from oxo, hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alcohol, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $CONR^{11}R^{12}$, $NR^{11}SO_2R^{12}$, $NR^{11}COR^{12}$, C_0-C_3 alkyl$NR^{11}R^{12}$, C_1-C_3 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, cyano, and phenyl, and wherein two R^2 groups may combine to form a 3,4 or 5 member spirocycle, or a five or six member fused carbocyclic or heterocyclic ring;

R^3 is hydrogen, C_1-C_6 alkyl, aryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, C_3-C_8 cycloalkyl, or C_1-C_6 alkylcycloalkyl;

R^4 is hydrogen, C_1-C_6 alkyl, aryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl or a group represented by the formula -NR^9R^{10};

R^5 is selected from the group consisting of hydrogen, hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, aryl, C_1-C_6 alkylaryl, heteroaryl, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -NR^7R^8, and -OC_1-C_6 alkylaryl; and wherein when q is 1, 2 or 3, two adjacent R5 groups may combine to form a fused 5 or 6 member optionally substituted carbocyclic or heterocyclic ring;

R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, C_1-C_6 alkylNR^7R^8, C_3-C_8 cycloalkyl, and C_1-C_6 alkylcycloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, C_1-C_6 alkyheterocyclic, heterocyclic, aryl, C_1-C_6 alkylaryl, wherein each alkyl, heterocyclic, or aryl group is optionally substituted with 1-3 groups independently selected from halogen, C_1-C_6 alkycylcloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylheterocyclic, C_1-C_6 haloalkyl, and $NR^{11}R^{12}$; or R^7 and R^8 combine to form a nitrogen containing heterocyclic ring which may have 0,

1, or 2 additional hetero-atoms selected from oxygen, nitrogen or sulfur and may be optionally substituted with oxo, or C_1-C_6 alkyl;

R^9 is the group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, aryl, heterocyclic, C_1-C_6 alkylheterocyclic, COR^7, CO_2R^7, $CONR^7R^8$, $S(O)_pNR^7R^8$, or $S(O)_pR^7$ wherein R^7 is as defined above, and wherein each alkyl, cycloalkyl, aryl, and heterocyclic is optionally substituted with one to two groups independently selected from halo, hydroxy, oxo, COOH, $C(O)OC_1$-C_4 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylalcohol, C_1-C_6 alkylamine, C_1-C_6 alkylaryl, C_2-C_6 alkenylaryl, C_2-C_6 alkynylaryl, C_1-C_6 alkylheterocyclic, $-NR^7R^8$, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, C_1-C_6 alkyl-O-C_1-C_6 alkylaryl, C_1-C_6 alkyl-NR^2-C_1-C_6 alkylaryl, and aryl, wherein each cycloalkyl or aryl group is optionally substituted with halo, hydroxy, oxo, amino, COOH, $C(O)OC_1$-C_4 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylalcohol, and C_1-C_6 alkyalmine;

R^{10} is selected from the group consisting of aryl, C_1-C_6 alkylaryl, C_2-C_6 alkenylaryl, C_2-C_6 alkynylaryl, C_1-C_6 haloalkylaryl, C_1-C_6 alkylheterocyclic, C_2-C_6 alkenylheterocyclic, C_1-C_6 alkylcycloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkyl-O-C_1-C_6 alkylaryl, and wherein each cycloalkyl, aryl, or heterocyclic group is optionally substituted with 1-3 groups independently selected from the group consisting of hydroxy, oxo, $-SC_1$-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 haloalkyl, halogen, C_1-C_6 alkoxy, aryloxy, C_1-C_6 alkenyloxy, C_1-C_6 haloalkoxyalkyl, C_0-C_6 alkyl$NR^{11}R^{12}$, $-OC_1$-C_6 alkylaryl, nitro, cyano, C_1-C_6 haloalkylalcohol, and C_1-C_6 alkylalcohol;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl, heterocyclic, aryl, and C_1-C_6 alkylaryl, wherein each aryl group is optionally substituted with 1-3 groups independently selected from halogen, C_1-C_6 alkylheterocyclic, and C_1-C_6 haloalkyl, or R^{11} and R^{12} combine to form a nitrogen containing heterocyclic ring which may have 0, 1, or 2 additional heteroatoms selected from oxygen, nitrogen or sulfur and is optionally substituted with oxo, or C_1-C_6 alkyl; or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

2. A compound according to Claim 1 wherein R^1 is selected from a group consisting of C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -OC_3-C_8 cycloalkyl, -OC_1-C_6 alkylaryl, and -OC_1-C_6 alkylheterocyclic.

3. A compound according to Claim 1 wherein R^4 is NR^9R^{10} and R^9 is a heterocyclic group optionally substituted with one to two groups independently selected from halo, amino, C(O)OC_1-C_4 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylalcohol, C_1-C_6 alkyalmine, C_3-C_8 cycloalkyl, and C_1-C_6 alkylcycloalkyl.

4. A compound according to Claim 1 wherein j is 0, or 1.

5. A compound of claim 1 wherein j is 2.

6. A compound of claim 1, wherein j is 0, or 1 or 2; n is 0 or 1; m is 0, and q is 0.

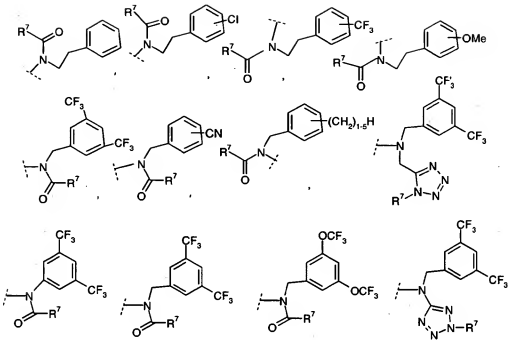
7. A compound according to Claim 1 wherein n, m, and q are independently 0, or 1.

8. A compound according to Claim 1 wherein the A ring is selected from the group consisting of pyridine, pyrazine, thiophene, pyrazole isoxazole, oxazole, and thiazole.

9. A compound according to Claim 1 wherein the A ring is pyridine.

10. A compound according to Claim 1 wherein the A ring is thiophene.

11. A compound according to Claim 1 wherein R^3 is hydrogen and R^4 is NR^9R^{10} selected from the group consisting of:



12. A compound according to Claim 1 wherein R^4 is NR^9R^{10} and R^9 is $COOR^7$.

13. A compound according to Claim 1 wherein R^4 is NR^9R^{10} and R^9 is $CONR^7R^8$.

14. A compound according to Claim 1 wherein R^4 is NR^9R^{10} and R^9 is $S(O)_2NR^7R^8$.

15. A compound according to Claim 1 wherein R^3 or R^4 is NR^9R^{10} and R^9 is $S(O)R^7$.

16. A compound selected from the group consisting of:
4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,
4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-3,4-dihydro-2H-[1,7]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-3,4-dihydro-2H-[1,6]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-methyl-2-ethyl-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5-ethyl-3,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-4-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5-ethyl-2,5,6,7-tetrahydro-pyrazolo[4,3-b]pyridine-4-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5-ethyl-6,7-dihydro-5H-2-thia-4-aza-indene-4-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-5,6-dihydro-4H-thieno[2,3-b]pyridine-7-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-5,6-dihydro-4H-isoxazolo[5,4-b]pyridine-7-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-3-trifluoromethyl-5,6-dihydro-4H-isoxazolo[5,4-b]pyridine-7-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-3-methyl-5,6-dihydro-4H-isoxazolo[5,4-b]pyridine-7-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-3-isopropyl-5,6-dihydro-4H-isoxazolo[5,4-b]pyridine-7-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-ethyl-6,7-dihydro-5H-pyrido[2,3-d]pyrimidine-8-carboxylic acid isopropyl ester,

8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6-ethyl-7,8-dihydro-6H-pyrido[2,3-b]pyrazine-5-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-bromo-5-ethyl-6,7-dihydro-5H-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester,

7-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-trifluormethyl-5-ethyl-6,7-dihydro-5H-thieno[3,2-b]pyridine-4-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-chloro-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-methyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-trifluoromethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-methoxy-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-methyl-3,4-dihydro-2*H*-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-7-chloro-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-4,5,6,7-tetrahydro-thieno[2,3-b]azepine-8-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-bromo-4,5,6,7-tetrahydro-thieno[2,3-b]azepine-8-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3-trifluoromethyl-4,5,6,7-tetrahydro-thieno[2,3-b]azepine-8-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-thieno[3,4-b]azepine-1-carboxylic acid isopropyl ester,

8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3-methyl-5,6,7,8-tetrahydro-thieno[3,2-b]azepine-4-carboxylic acid isopropyl ester,

8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-bromo-5,6,7,8-tetrahydro-thieno[3,2-b]azepine-4-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-4,5,6,7-tetrahydro-pyrazolo[2,3-b]azepine-8-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-4,5,6,7-tetrahydro-isoxazolo[5,4-b]azepine-8-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-pyrido[2,3-b]azepine-9-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-pyrido[3,4-b]azepine-1-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-pyrido[4,3-b]azepine-1-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-pyrido[3,2-b]azepine-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-trifluoromethyl-6,7,8,9-tetrahydro-pyrido[3,2-b]azepine-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3-trifluoromethyl-6,7,8,9-tetrahydro-pyrido[3,2-b]azepine-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-1,4,5-triaza-benzocycloheptene-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-trifluoromethyl-6,7,8,9-tetrahydro-1,4,5-triaza-benzocycloheptene-5-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-chloro-6,7,8,9-tetrahydro-1,4,5-triaza-benzocycloheptene-5-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-pyrimido[4,5-b]azepine-9-carboxylic acid isopropyl ester,

8-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-3H-1,3,4-triaza-azulene-4-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-3,5,6,7,8,9-hexahydro-1,3,4-triaza-cyclopentacyclooctene-4-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-1,4,5,6,7,8-hexahydro-1,2,9-triaza-cyclopentacyclooctene-9-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-4H-1-oxa-2,9-diaza-cyclopentacyclooctene-9-carboxylic acid isopropyl ester,

4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-5,6,7,8-tetrahydro-4H-thieno[2,3-b]azocine-9-carboxylic acid isopropyl ester,

9-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-5H-2-thia-4-aza-cyclopentacyclooctene-4-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-5H-1,10-diaza-benzocyclooctene-10-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-5H-2,10-diaza-benzocyclooctene-10-carboxylic acid isopropyl ester,

10-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7,8,9,10-tetrahydro-6H-2,5-diaza-benzocyclooctene-5-carboxylic acid isopropyl ester,
10-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7,8,9,10-tetrahydro-6H-1,5-diaza-benzocyclooctene-5-carboxylic acid isopropyl ester,
10-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7,8,9,10-tetrahydro-6H-1,4,5-triaza-benzocyclooctene-5-carboxylic acid isopropyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-6,7,8,9-tetrahydro-5H-1,3,10-triaza-benzocyclooctene-10-carboxylic acid isopropyl ester,
Cis-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester ,
Cis-4-[(3,5-bis-trifluoromethyl-benzyl)-(2*H*-tetrazol-5-yl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester,
Cis-4-[(3,5-bis-trifluoromethyl-benzyl)-(2-methyl-2*H*-tetrazol-5-yl)-amino]-2-ethyl-6-methoxy-3,4-dihydro-2H-[1,5]naphthyridine-1-carboxylic acid isopropyl ester,
or a pharmaceutically acceptable salt, solvate enantiomer or diastereomer or mixture thereof.

17. A method of regulating CETP activity comprising administering a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof to a patient in need thereof.

18. A method of treating or preventing dyslipidemia comprising administering a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers thereof, to a patient in need thereof.

19. A method of treating or preventing artherosclerosis comprising administering a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient.

20. A method according to Claim 18, wherein the regulation of CETP activity results in a decrease in LDL-cholesterol.

21. A method of lowering plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient in need thereof.

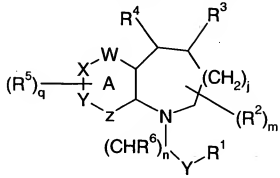
22. A method of treating and/or preventing the pathological sequelae due to high levels of plasma LDL-cholesterol in a mammal comprising administering an effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers to a patient in need thereof.

23. A pharmaceutical composition comprising a compound according to Claim 1 and a carrier, diluent and/or excipient.

24. Use of a compound of formula I for the manufacture of a medicament for treating and/or preventing atherosclerosis in a mammal comprising administering an effective dose of a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient in need thereof.

Abstract

The present invention discloses compounds of formula I



wherein A, n, m, j, q, y, W, X, Y, Z, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined herein and their pharmaceutical compositions and methods of use are disclosed as useful for treating dyslipidemia and its sequelae.